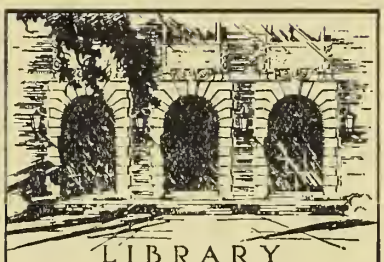


SEMINAR TOPICS

I Semester 1946-47

Cwl

AUTOXIDATION OF PARAFFINIC HYDROCARBONS

This report is based chiefly on Zuidema's review (1) of the oxidation of lubricating oils. He points out that the oxidation of paraffinic hydrocarbons has been studied principally from two points of view. The chief interest of manufacturers of lubricating oils has been in a search for ways to prevent oxidation. Other investigators, especially in Germany and in Russia, have sought to control the oxidation so that it might be used to produce oxygen-containing compounds such as alcohols, carbonyl compounds, acids, and esters. Organic molecules of many types undergo autoxidation although in most instances the reaction is very slow at ordinary temperatures. The initial products appear to be peroxides and are always more reactive than the parent compound. Consequently the reaction is difficult to control and usually leads to a wide variety of products. The conversion of a paraffin to fatty acids, for example, presumably involves the intermediate formation of a hydroperoxide, a carbonyl compound, and other more complex substances.

It would appear that autoxidation is a characteristic reaction of compounds containing active CH, CH_2, or CH_3 groups and that the rate of the oxidation is proportional to the reactivity of the C-H bond in question. In support of this it is known that an alkyl side chain on an aromatic ring is attacked exclusively at the methylene group next to the ring. A well-known example of this behavior is the formation of the peroxide of tetralin (2).

To compare the reactivity at a tertiary carbon atom with that of primary or secondary carbon atoms Chavanne and Bode (3) studied the autoxidation of 1,4-dimethylcyclohexane. At 100° 116 g. of the hydrocarbon absorbed 30.7 g. of oxygen rapidly, yielding 1,4-dimethylcyclohexanol as the chief product (30 g.). Other products include water, carbon dioxide (5.2 g.), β-methyl-δ-acetylvaleric acid (8-9 g.), acetic acid (4-5 g.), β-methylvaleric acid (2-3 g.), dimethylcyclohexanediol (5.5 g.), and acetonylacetone (0.5 g.). Small amounts of hydrogen, carbon monoxide, methane, ethane, and formic acid were also detected. These results show that reaction occurred at the tertiary carbon atom, the initial hydroperoxide being reduced to the corresponding alcohol or oxidized to open chain compounds.

A comparison of the reactivity at primary and secondary carbon atoms was made by a study of normal paraffins (3,4,5). It was shown that oxidation of n-decane, n-nonane, and n-octane with oxygen at atmospheric pressure and at a temperature of 120° produced preponderant amounts of the corresponding methyl ketones as well as a series of carboxylic acids ranging from formic to C_{n-1}, where n is the number of carbon atoms in the hydrocarbon. These data indicate that the attack of oxygen is not at the primary (terminal) but at a secondary carbon atom. The beta carbon atom is involved primarily, the gamma secondarily, and so on to the middle of the chain. Thus formic, acetic, and propionic acids would be expected in the order of decreasing concentration. A study of the oxidation of lubricating oils (6,7) has confirmed this prediction.

Prior to the outbreak of World War II much attention had been given to the problem of making higher fatty acids by air oxidation of higher paraffins. Many processes had been patented which indicated the procedure to be feasible at least for making soaps. The standard procedures involve blowing air through a mixture of hydrocarbons. During the war the Germans used this method to manufacture fatty acids on a large scale. The fatty acids were separated by careful fractionation. It is reported that acids from C_1 to C_{24} were made available by this development (8).

The Russians have described many attempts to produce fatty acids from paraffin wax and paraffinic oil fractions. For example, Varlamow (9) found that in oxidation of a Grozny paraffin at 160-180° with air at 15-30 atmospheres 20 to 74 per cent of the paraffin reacted and 70 per cent or more of the reaction products were fatty acids.

In an attempt to develop a commercial method for producing higher alcohols Hass, McBee, and Churchill (10) oxidized hexadecane with air under a pressure of 2000 pounds per square inch at temperatures from 190° to 300°. The product, which contained alcohols, acids, esters, and carbonyl compounds, was hydrogenated, yielding a mixture of alcohols having an average molecular weight as high as 165. Conversions for the two-step process were as high as 17 per cent.

Bibliography

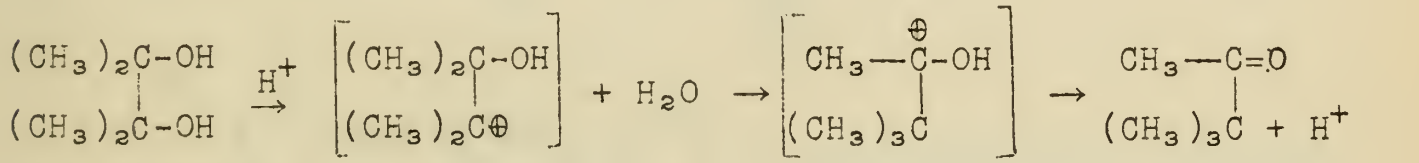
1. Zuidema, Chem. Rev., 38, 197 (1946).
2. Hock and Susemihl, Ber., 66B, 61 (1933).
3. Chavanne and Bode, J. Am. Chem. Soc., 52, 1609 (1930).
4. Chavanne and Tock, Bull soc. chim. Belg., 41, 630 (1932).
5. Dupont and Chavanne, Bull soc. chim. Belg., 42, 537 (1933).
6. Fenske, Stevenson, Lawson, Herbolsheimer, and Koch, Ind. Eng. Chem., 33, 516 (1941).
7. Fenske, Stevenson, Rusk, Lawson, Cannon, and Koch, Ind. Eng. Chem., Anal. Ed., 13, 51 (1941).
8. Ind. Eng. Chem., News Ed., 23, 1516 (1945).
9. Varlamow, Maslaboino Shirovoe Delo. 1932, No. 4-5, 41; No. 6, 47; Chem. Abs., 27, 3595 (1933).
10. Hass, McBee, and Churchill, Ind. Eng. Chem., 37, 445 (1945).

Reported by R. C. Fuson
October 4, 1946

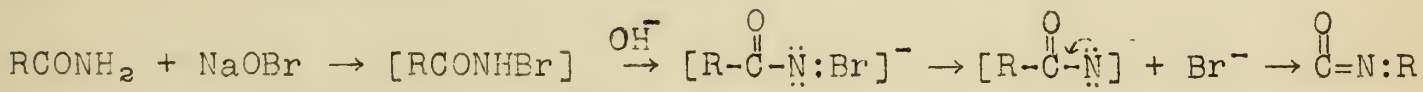
CARBONIUM-LIKE INTERMEDIATES IN MOLECULAR REARRANGEMENTS

There are a number of apparently unrelated transformations and rearrangements which involve a change in the carbon skeleton of a molecule. They are the Wagner-Meerwein rearrangement, the Hoffman degradation of amides, the Beckmann rearrangement, the benzilic acid rearrangement, the Curtius degradation, the pinacol rearrangement, paraffin isomerization, the Wolff rearrangement, the Schmidt reaction, and ring expansion with diazomethane, to mention a few of the best known examples.

All of these reactions may be embraced within a single reaction mechanism if it is supposed that a carbonium ion or an atom with only six electrons is formed as an intermediate and that the formation of this intermediate is followed by the shift of an alkyl group from an adjacent carbon atom in accordance with the Whitmore theory. Thus the pinacol rearrangement might be written:



and the Hoffman rearrangement:



Evidence supporting this view includes in some cases kinetics, solvent effects, and the behavior of the reactions upon the addition of electrophilic reagents. It is interesting, however, that whenever optical isomers are involved configuration is almost always retained. This implies that if such fragments are formed during the reaction they must have an extremely short life and that they must still be subject to other molecular influences.

Bibliography

1. Hammett, "Physical Organic Chemistry", pp. 317-325.
2. Whitmore, et al., J. Amer. Chem. Soc., 1932-1938.
3. Bartlett and Pöckel, ibid., 60, 1585 (1938).
4. Pines and Wackler, ibid., 68, 602 (1946).
5. Taylor and Baker, "Sidgwicks Organic Chemistry of Nitrogen", pp. 370, 360-365.

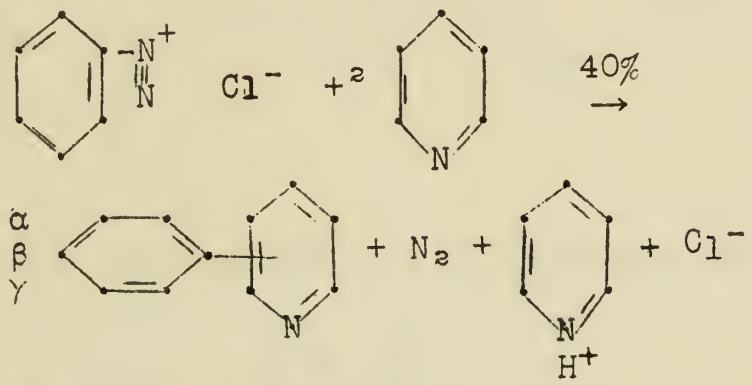
Reported by E. R. Alexander
October 11, 1946

ARYLPYRIDINES

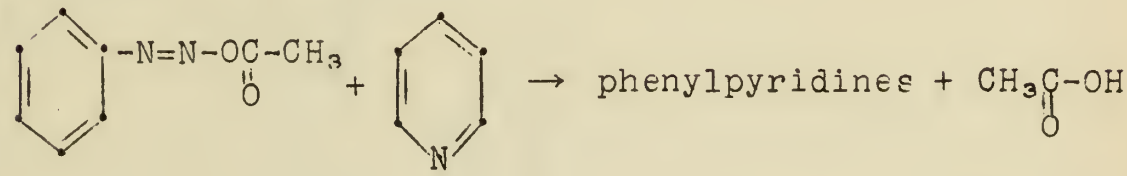
Since 1893 (1) when the first aryl derivative of pyridine was reported, a substantial number of arylpyridines have been synthesized by several different methods:

A. Reaction of pyridine with diazonium salts or alkali or acetyl diazotates (1,2,3,4,5,11,14,15,16).

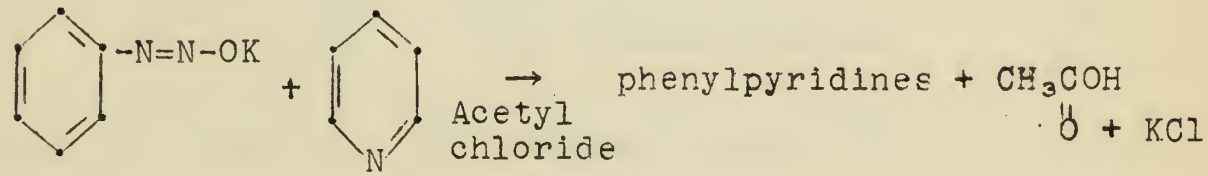
1.



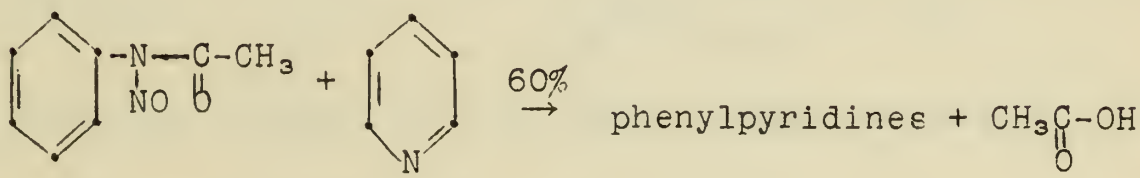
2.



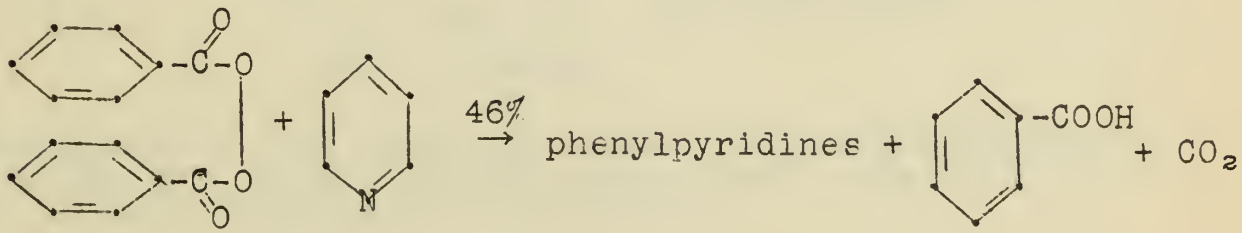
3.



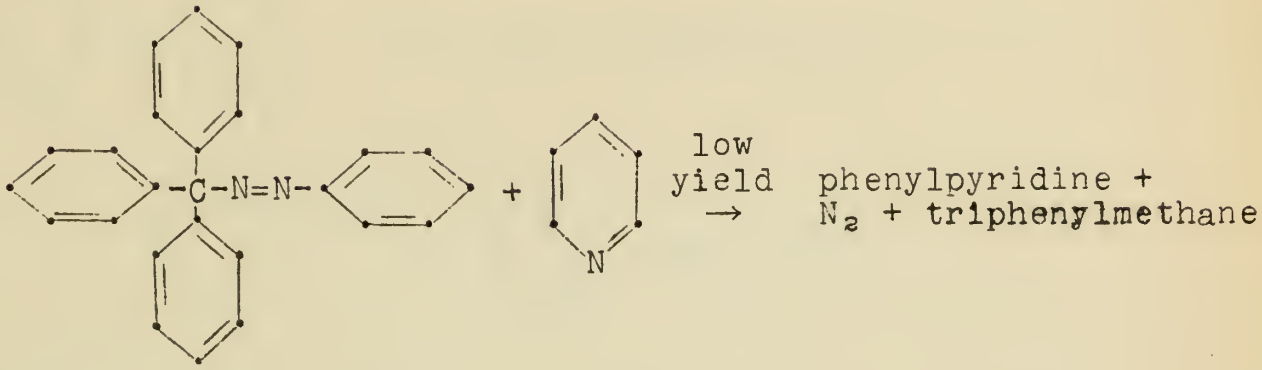
B. Reaction of pyridine with nitosoacylarylamines (2,3,4,14,19).



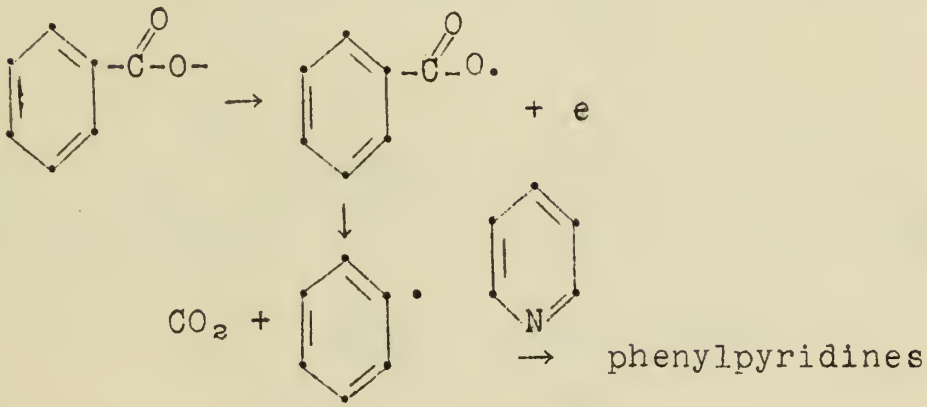
C. Reaction of pyridine with benzoyl peroxide (6).



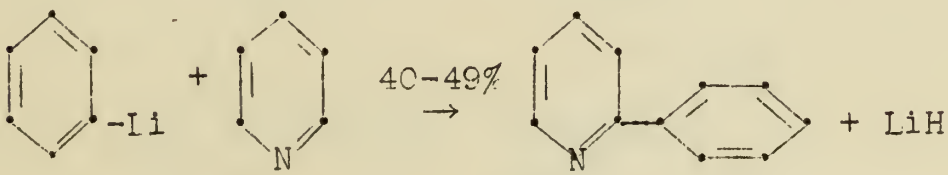
D. Reaction of pyridine with triphenylmethylazobenzene (7).



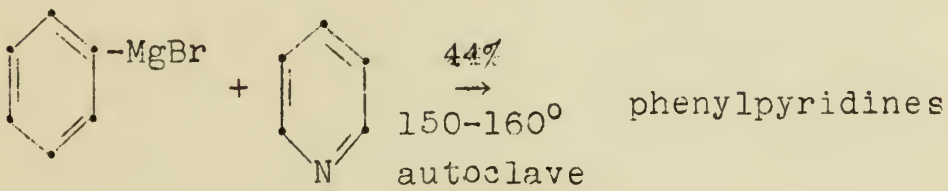
E. Kolbe electrosynthesis in pyridine (9).



F. Reaction of pyridine with phenyllithium (13).

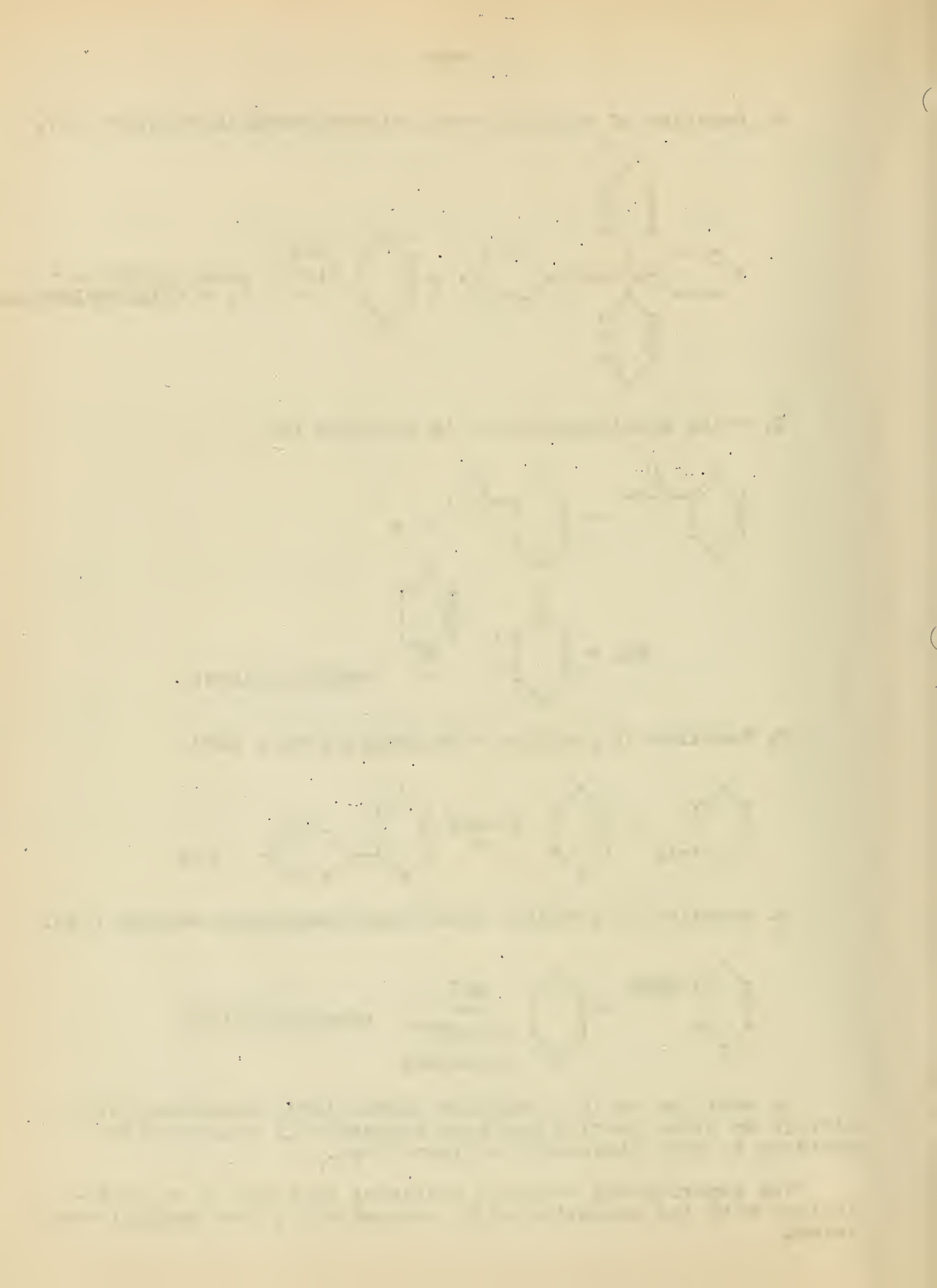


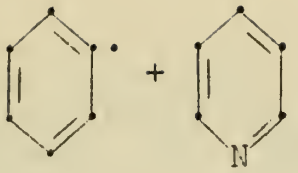
G. Reaction of pyridine with phenyl magnesium bromide (12).



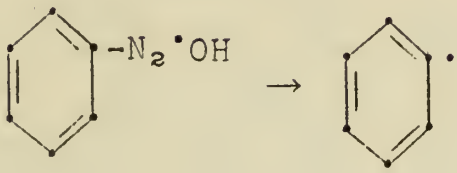
In addition to the compounds listed (19), 4-aminophthalonitrile on diazotization has been successfully reacted with pyridine to form dicyanophthalylpyridines.

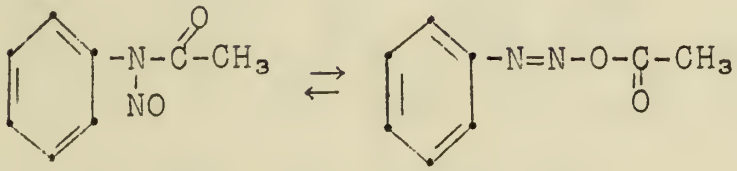
The experimental evidence indicates that all of these reactions with the exception of F, proceed via a free radical mechanism.

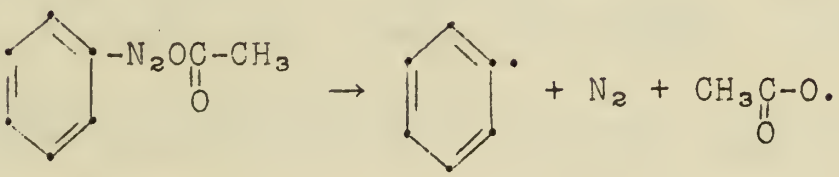




→ γ, β, and γ-phenylpyridines + H.



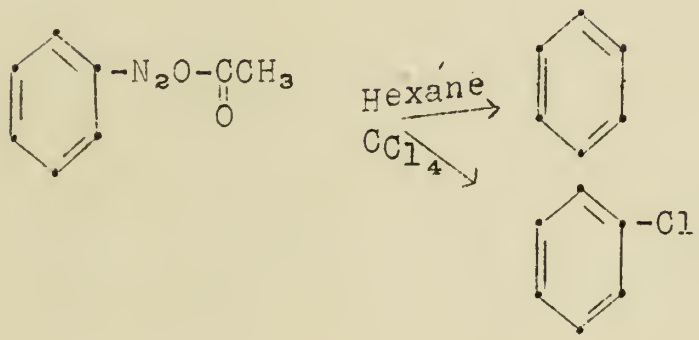




$$CH_3\overset{\overset{O}{\|}}{C}O. \rightarrow CO_2 + CH_3.$$

$$CH_3. + H. \rightarrow CH_4$$

$$CH_3\overset{\overset{O}{\|}}{C}O. + H. \rightarrow CH_3\overset{\overset{O}{\|}}{C}\text{-OH}$$



Bibliography

1. Möhlau and Berger, Ber. 26, 1994 (1893).
2. Kühling, Ber., 28, 41, 523 (1895).
3. Bamberger, Ber., 28, 403 (1895); 30, 366 (1897).
4. Kühling, Ber., 29, 165 (1896).
5. Gomberg and Bachmann, J. Amer. Chem. Soc., 46, 2339 (1924).
6. Overhoff and Tilman, Rec. Trav. Chimie, 48, 993 (1929).
7. Wieland, et al., Ann., 514, 155 (1934).
8. Hey and Waters, Chem. Reviews, 21, 169 (1937).
9. Fichter and Stanzl, Helv. Chim. Acta., 22, 970 (1939).
10. Hey, Annual Reports, 37, 278 (1940).
11. Forsyth and Pyman, J. Chem. Soc., 1926, 2912.
12. Berstrom and McAllister, J. Amer. Chem. Soc., 52, 2845 (1930).
13. Walters and McElvain, J. Amer. Chem. Soc., 55, 4625 (1933).
14. Haworth, Heilbron and Hey, J. ~~Amer~~. Chem. Soc., 1940, 349, 356, 372.
15. Haworth and Hey, J. Chem. Soc., 1940, 361.
16. Heilbron, Hey and Lambert, J. Chem. Soc., 1940, 1279.
17. Coates, Cook, Heilbron, Hey, Lambert and Lewis, J. Chem. Soc., 1943, 410.
18. Hey, Annual Reports, 41, 181 (1944).
19. Organic Reactions, II, 224 (1944). See Table pages 260-1.

Reported by L. E. Miller
October 11, 1946

SOME REACTIONS OF THE DISULFIDE LINKAGE IN WOOL

Several of the more important physical and chemical properties of wool are related directly to the presence of disulfide cross-linkages between polypeptide chains of the protein. This conclusion is the result of a study of the chemical and physical properties of wool before and after alteration of the sulfur linkage by a series of highly specific chemical reactions (1,2,3,4,5).

The cystine in wool can be readily reduced to cysteine with thioglycolic acid. Although strongly alkaline solutions of the reagent have been shown to dissolve the protein, the reaction may be carried out in neutral or acid solution without destruction of the wool fibers. By this treatment the disulfide links are

$$W\text{-}S\text{-}S\text{-}W + 2HSCH_2CO_2H \rightarrow 2W\text{-}SH + (SCH_2CO_2H)_2 \qquad (W = \text{wool})$$

reduced to sulfhydryl groups, which may then be reacted with alkyl halides to form thioether groups. While reduced wool is readily

$$W\text{-}SH + RX \rightarrow W\text{-}S\text{-}R + HX$$

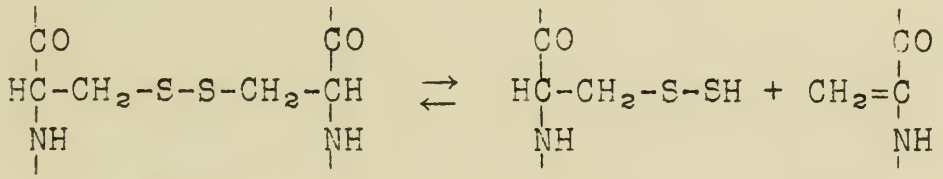
reoxidized thus regenerating the original material, alkylated wo (W-S-R) is stable to oxidizing agents and can be handled without danger of reestablishing the cross-links. Fibers of this type a much more extensible and weaker than the original wool. Alkylat with aliphatic dihalides, such as methylene iodide or trimethyle dibromide, introduces hydrocarbon chains between sulfur atoms of the resulting wool. Such fibers are similar to untrested fibers in physical properties.

$$W\text{-}SH + X(CH_2)_nX \rightarrow W\text{-}S(CH_2)_nS\text{-}W + 2HX$$

Wool in which the disulfide links have been broken by reduction possesses much higher alkali-solubility than untreated wool. Although the creation of sulfhydryl groups along the polypeptide chain undoubtedly contributes to the alkali-solubility, the principle cause is thought to be the destruction of the three-dimensional structure of the wool. As contributory evidence in support of this theory it has been found that reduced wool which has been alkylated with a monohalide also has a high alkali-solubility, although it contains no sulfhydryl groups. Wool having the sulfur atoms separated by a carbon chain [$W\text{-}S(CH_2)_nS\text{-}W$] has a much lower alkali-solubility.

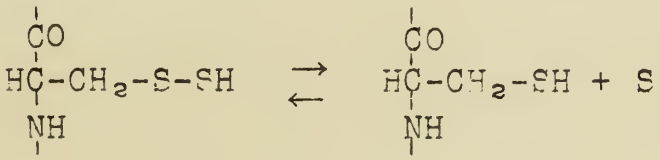
The disulfide linkage appears to contribute to the resistance of the wool to attack by enzymes. Thus wool which has neither been injured mechanically nor modified chemically is completely resistant to attack by proteolytic enzymes - pepsin, trypsin, chymotrypsin, and papain. Wool in which the disulfide cross-linkages have been broken, as by reduction, or wool in which reduction is followed by methylation, is almost completely digested by pepsin. When reduced wool is reoxidized, it regains its original stability, and when bis-thioether groups are introduced by action of an aliphatic dihalide on the sulfhydryl groups, the stability of the wool toward enzymes is greatly enhanced.

The action of alkalies on wool is very important from a commercial point of view since wool is often scoured in alkaline soaps and is frequently bleached in alkaline medium. Even mild alkali has a detrimental effect on the strength of the fibers, and much could be gained by development of any means for improving the stability of wool to alkaline agents. Investigations of the course of the reaction of cystine in wool and similar proteins with alkali has revealed that one atom of sulfur is split from each molecule of cystine (6,7,8,9,10). Of the residual non-cystine sulfur in alkali-treated wool, more that 25 per cent has been accounted for as lanthionine after hydrolysis. No significant amounts of sulfhydryl groups have been found in alkali-treated wools. Recent results lead to the conclusion that the alkali cleavage of the disulfide group does not consist primarily in hydrolytic rupture between the sulfur atoms with the formation of a sulfhydryl compound and a sulfenic acid as was first postulated. Rather, the evidence is more consistent with mechanism advanced by Nicholet and Shinn (11), which involves a rupture between sulfur and carbon atoms to yield dehydroalanine and a $-CH_2-S-SH$ residue. An atom of sulfur is eliminated from the latter, and the -SH group thus formed reacts with dehydroalanine to form lanthionine.



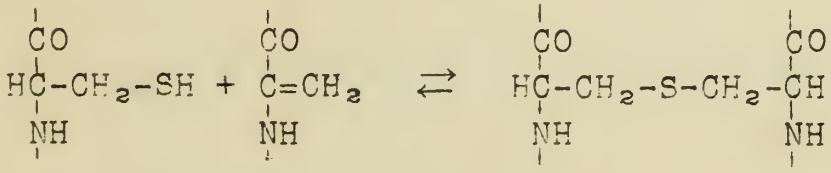
Wool — Dehydroalanine

Then:



Cysteine

And:



Cysteine — Dehydro-alanine — Lanthionine

Bibliography

1. Patterson, Geiger, Mizell, Harris, J. Research Natl. Bur. Stds., 27, 89 (1941).
2. Harris, Mizell, Fourt, Ind. Eng. Chem., 34, 833 (1942).
3. Geiger, Kobayashi, Harris, J. Research Natl. Bur. Stds., 29, 381 (1942).
4. Geiger, Patterson, Mizell, Harris, J. Research Natl. Bur. Stds., 27, 459 (1941).
5. Geiger, Harris, J. Research Natl. Bur. Stds., 29, 271 (1942).
6. Speakman, Whewell, J. Soc. Dyers and Colourists, 52, 380 (1936).
7. Speakman, Whewell, J. Soc. Dyers and Colourists, 52, 335 (1936).
8. Crowder, Harris, J. Research Natl. Bur. Stds., 15, 63 (1935).
9. Crowder, Harris, J. Research Natl. Bur. Stds., 16, 475 (1936).
10. Mizell, Harris, J. Research Natl. Bur. Stds., 30, 47 (1943).
11. Nicholet, Shinn, J. Am. Chem. Soc., 63, 2284 (1941).

Geiger, Kobayashi, Harris, Ind. Eng. Chem., 34, 1398 (1942).

Harris, Textile Research, 12, 19 (1941).

Harris, Mizell, Fourt, J. Research Natl. Bur. Stds., 29, 73 (1942).

Horn, Jones, Ringel, J. Biol. Chem., 138, 141 (1941).

Patterson, Geiger, Mizell, Harris, Textile Research, 11, 379 (1940).

Reported by N. A. Higgins
October 18, 1946

α,β-ACETYLENIC KETONES

Bowden, Heilbron, and coworkers (4) have reported recently on a new and convenient synthesis for acetylenic ketones consisting of chromic acid oxidation of the corresponding secondary alcohols. This makes available a relatively new class of compounds, the ethynyl ketones, HC≡C-CO-R. A study of the properties of these ketones and the more general class of α,β-acetylenic ketones, R-C≡C-CO-R', brings to light many interesting compounds and reactions of potential value in synthesis.

I. SYNTHESIS

With the exception of the oxidation method mentioned above there appear to be few routes of general applicability for obtaining α,β-acetylenic ketones and related keto-compounds (4). Those sources which have been listed are as follows.

(1) From alkali metal acetylides and acyl halides (1,23), esters (26,27,35), or acid anhydrides (29), thus,

$$R\text{-}C{\equiv}C\text{-}Na + R'\text{-}COCl \rightarrow R\text{-}C{\equiv}C\text{-}CO\text{-}R' + NaCl$$

(2) From acetylenic Grignard reagents and acyl halides, acid anhydrides (18), and α-chloroketones (32,33), thus,

$$R\text{-}C{\equiv}C\text{-}MgX + R'\text{-}CO_2R'' \rightarrow R\text{-}C{\equiv}C\text{-}CO\text{-}R' + R''O\text{-}MgX$$

(3) From phenyl propiolic esters and phenyl magnesium bromide (14),

$$C_6H_5C{\equiv}C\text{-}CO_2Et + C_6H_5MgBr \rightarrow C_6H_5C{\equiv}C\text{-}CO\text{-}C_6H_5 + EtO\text{-}MgBr$$

(4) By partial hydration of conjugated diacetylenes (11,12).

$$R\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}R' + H_2O \rightarrow R\text{-}CH_2\text{-}C{\equiv}C\text{-}CO\text{-}R'$$

(5) By Friedel-Crafts reactions with substituted propioli chlorides (17,31),

$$R\text{-}C{\equiv}C\text{-}COCl + R'H \xrightarrow{AlCl_3} R\text{-}C{\equiv}C\text{-}CO\text{-}R' + HCl$$

(6) By oxidation of secondary acetylenic carbinols wi). chromic acid (4, 8,19) with acetone as the usual solvent,

$$R\text{-}\underset{OH}{CH}\text{-}C{\equiv}C\text{-}R' \xrightarrow[\text{Acetone}]{CrO_3 + HOAc} R\text{-}CO\text{-}C{\equiv}C\text{-}R'$$

$$R\text{-}\underset{OH}{CH}\text{-}C{\equiv}C\text{-}\underset{OH}{CH}\text{-}R' \xrightarrow[\text{Acetone}]{CrO_3 + HOAc} R\text{-}CO\text{-}C{\equiv}C\text{-}CO\text{-}R$$

$$R\text{-}C{\equiv}C\text{-}\underset{OH}{CH}\text{-}C{\equiv}C\text{-}R' \xrightarrow[\text{Acetone}]{CrO_3 + HOAc} R\text{-}C{\equiv}C\text{-}CO\text{-}C$$

Ethynyl ketones (4) are formed by this method,

$$R\text{-}\underset{\underset{OH}{|}}{CH}\text{-}C{\equiv}CH \xrightarrow[HOAc]{CrO_3} R\text{-}CO\text{-}C{\equiv}CH$$

The acetylenic carbinols are made by a number of previously described methods (7,9,13,16,20).

Only one record of an ethynyl ketone synthesized by a different method was found (30). This involved acid hydrolysis of the enol methyl ether,

$$HC{\equiv}C\text{-}\underset{\underset{OCH_3}{|}}{C}{=}CH_2 + H_2O \xrightarrow{H_2SO_4} HC{\equiv}C\text{-}CO\text{-}CH_3 + CH_3OH$$

The enol methyl ether used in this case was derived from 1-Bromobutadiene.

Some examples of various α,β-acetylenic ketones and keto-compounds which have been prepared by these methods, together with yields, are listed in the following table.

No.	Compound	Method	Yield	Ref.
1	$C_6H_5\text{-}C{\equiv}C\text{-}CO\text{-}CH_3$	1	55%	(29)
2	$C_6H_5\text{-}C{\equiv}C\text{-}CO\text{-}C_6H_5$	1,3,6	74-85%	(28,14,29)
3	$(5\text{-}CH_3)(2CH_3O)C_6H_3\text{-}CO\text{-}C{\equiv}C\text{-}C_6H_5$	5	80%	(31)
4	$C_4H_9C{\equiv}C\text{-}COCH_3$	2,6	58%	(18)
5	$C_6H_5C{\equiv}C\text{-}CO\text{-}CH{=}CH\text{-}CH_3$	1	49%	(29)
6	$H_2C{=}\underset{\underset{CH_3}{|}}{C}\text{-}C{\equiv}C\text{-}CO\text{-}CH_3$	6	25%	(4)
7	$H_2C{=}CH\text{-}C{\equiv}C\text{-}CO\text{-}CH_3$	6	16.5%	(4)
8	$(CH_3)_2\text{-}\underset{\underset{OH}{|}}{C}\text{-}C{\equiv}C\text{-}CO\text{-}CH{=}CH\text{-}CH_3$	6	60%	(4)
9	$(C_6H_5)_2\underset{\underset{OH}{|}}{C}\text{-}C{\equiv}C\text{-}CO\text{-}CH{=}CH\text{-}CH_3$	6	96%	(4)
10	$C_6H_5C{\equiv}C\text{-}CO\text{-}CH{=}CH\text{-}C_6H_5$	1	34%	(29)
11	$HC{\equiv}C\text{-}CO\text{-}CH_3$	6	40%	(4,30)
12	$HC{\equiv}C\text{-}CO\text{-}C_6H_5$	6	80%	(4)
13	$HC{\equiv}C\text{-}CO\text{-}CH_2CH_2CH_3$	6	70%	(4)
14	$HC{\equiv}C\text{-}CO\text{-}CH{=}CH\text{-}CH_3$	6	75%	(4)
15	$CH_3CH{=}CHCO\text{-}C{\equiv}C\text{-}CO\text{-}CH{=}CH\text{-}CH_3$	6	40%	(4)
16	$CH_3CH_2CH_2\text{-}CO\text{-}C{\equiv}C\text{-}CO\text{-}CH_2CH_2CH_3$	6		(4)
17	$CH_3CH_2CH_2\text{-}CO\text{-}C{\equiv}C\text{-}\underset{\underset{OH}{|}}{CH}\text{-}CH_2CH_2CH_3$	6	60%	(4)
18	$C_6H_5CO\text{-}C{\equiv}C\text{-}CO\text{-}C_6H_5$	6	90%	(4)

II. REACTIONS

A. Stability (4).--(1) Most acetylenic ketones may be kept indefinitely at 0° in the presence of a little hydroquinone.

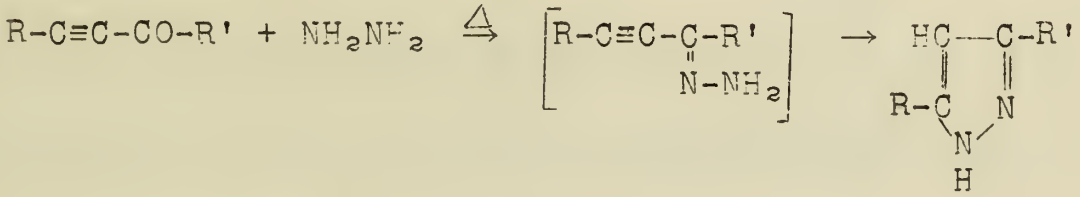
(2) In contrast to vinyl ketones, propyl ethynyl ketone was unaffected by heating with 1% benzoyl peroxide for 48 hours at 100°. Vinyl acetylenic ketones are unstable under these conditions.

B. Ethynyl Hydrogen (4).--(1) The ethynyl hydrogen readily attacks metallic copper and forms acetylides with ammoniacal cuprous and silver salts.

(2) It will liberate CH_4 quantitatively from CH_3MgI at ordinary temperatures.

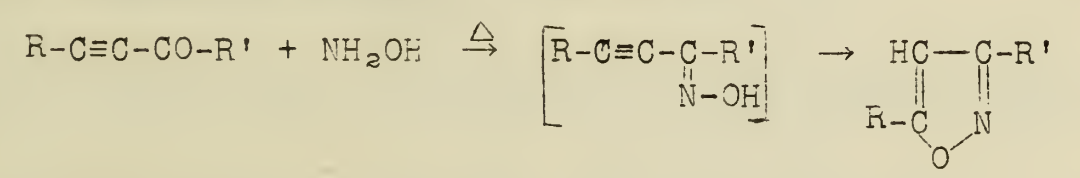
C. Carbonyl Function.--(1) All acetylenic ketones appear to form normal 2,4-dinitrophenylhydrazones (4).

(2) With hydrazine (1,21,25), however, substituted pyrazoles form,



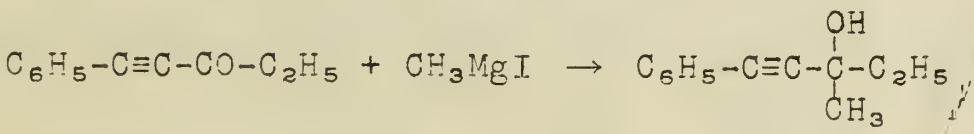
In this respect the acetylenic ketones resemble β-diketones.

(3) With NH_2OH (1,22,24,34), a similar cyclization takes place giving 3,5-disubstituted isoxazoles,



(A study of the reactions of ethynyl ketones with NH_2NH_2 and NH_2OH has not as yet been reported.)

(4) With RMgX, normal ketone addition can occur (6), but as in the case of the α,β-ethylenic ketones, the mode of addition varies with the nature of the compound (10).



D. Triple Bond Function.--(1) Addition of Amines (1,3,15). Both HC≡C-CO-R and R-C≡C-CO-R' add primary and secondary amines at the β-carbon.

$$HC{\equiv}C\text{-}CO\text{-}R + R_1R_2NH \rightarrow R_1R_2N\text{-}CH{=}CH\text{-}CO\text{-}R$$

$$R\text{-}C{\equiv}C\text{-}CO\text{-}R' + R_1NH_2 \rightarrow R_1NH\text{-}\underset{\displaystyle R}{\underset{|}{C}}{=}CH\text{-}CO\text{-}R'$$

Acid hydrolysis of the amine adducts give β-diketones, thus offering an indirect means of converting R-C≡C-CO-R' to R-CO-CH_2-CO-R'.

In ethylenic-acetylenic ketones, addition is invariably at the triple bond (3), e.g.,

$$CH_3CH{=}CH\text{-}CO\text{-}C{\equiv}CH + HNRR' \rightarrow CH_3CH{=}CH\text{-}CO\text{-}CH{=}CH\text{-}NRR'$$

(2) Addition of alcohols and phenols also occurs (23), thus,

$$C_6H_5C{\equiv}C\text{-}CO\text{-}C_3H_7 + C_2H_5OH \rightarrow C_6H_5\underset{\displaystyle OC_2H_5}{\underset{|}{C}}{=}CH\text{-}CO\text{-}C_3H_7$$

Dilute acid hydrolyzes such adducts to β-diketones, as in (1).

Heating of the adducts with NH_2OH gives the same disubstituted isoxazol as that obtained with R-C≡C-CO-R', thus,

$$\left.\begin{array}{c} C_6H_5\underset{\displaystyle OC_2H_5}{\underset{|}{C}}{=}CH\text{-}CO\text{-}C_2H_5 \\ \text{or} \\ C_6H_5C{\equiv}C\text{-}CO\text{-}C_2H_5 \end{array}\right\} \xrightarrow[NH_2OH]{\Delta} \begin{array}{l} HC\text{---}C\text{-}C_2H_5 \\ \quad\| \quad\quad \| \\ C_6H_5\text{-}C \quad N \\ \quad\quad \diagdown O \diagup \end{array}$$

(3) Condensation with dienes (5). Ethynyl ketones have been shown to function well as dienophils in Diels-Alder type additions,

$$CH_2{=}CH\text{-}CH{=}CH_2 + HC{\equiv}C\text{-}CO\text{-}R \xrightarrow{120^\circ} \begin{array}{l} \quad CH_2 \\ HC \quad\quad C\text{-}CO\text{-}R \\ \quad\| \quad\quad \| \\ HC \quad\quad CH \\ \quad CH_2 \end{array} \qquad 75\%$$

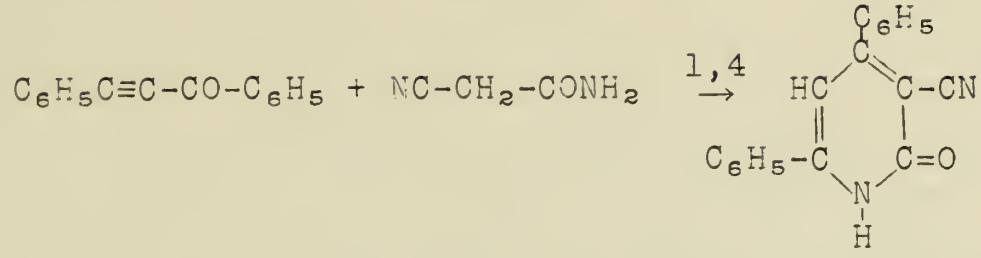
where R = CH_3 or C_6H_5

Propenyl ethynyl ketone can add two molecules of butadiene,

$$CH_3CH{=}CH\text{-}CO\text{-}C{\equiv}CH + CH_2{=}CH\text{-}CH{=}CH_2 \xrightarrow{100^\circ} CH_3CH{=}CH\text{-}CO\text{-}C\begin{array}{l} \quad CH_2 \\ \quad\| \\ H'C \quad CH \\ \quad\| \\ \quad CH_2 \end{array}$$

$$\xrightarrow[120\text{-}130^\circ]{\text{XS Butadiene}} \begin{array}{l} \quad CH_2 \quad\quad\quad CH_2 \\ HC \quad C\text{-}CO\text{---}C \quad\quad CH \\ \quad\| \quad\quad H \quad\quad\| \quad\quad\| \\ HC \quad C\text{-}CH_3 \quad C \quad\quad CH \\ \quad CH_2 \quad\quad H \quad\quad CH_2 \end{array}$$

(4) 1,4 Addition of cyanoacetamide (2),



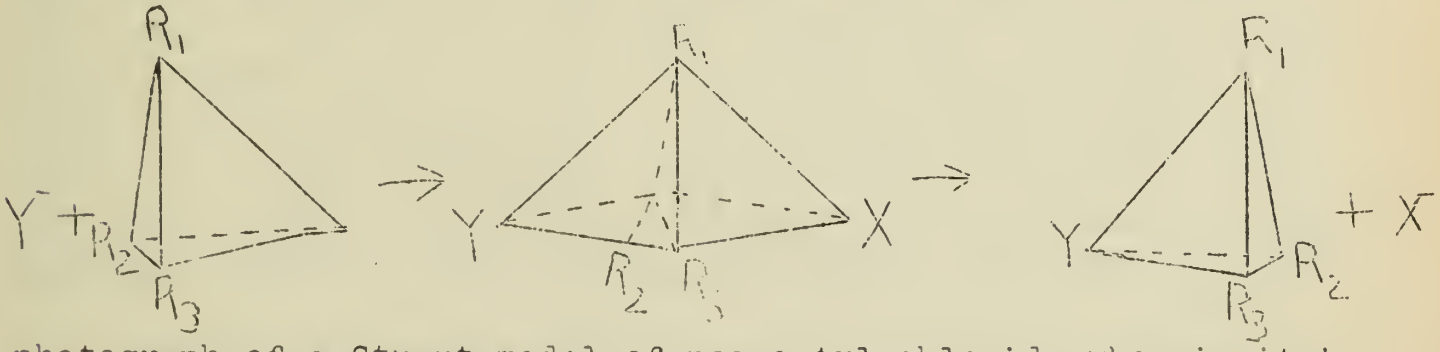
Bibliography

1. Andre, Ann. Chim., (8) 29, 557-568 (1913).
2. Barat, J. Ind. Chem. Soc., 7, 851-862 (1930); C. A., 25, 2145 (1931).
3. Bowden, Braude, Jones, and Weedon, J. Chem. Soc., 1946, 45-52.
4. Bowden, Helibron, Jones, and Weedon, ibid, 39-45.
5. Bowden and Jones, ibid, 52-54.
6. Brachin, Bull. Soc. Chim., (3), 35, 1176-1179 (1907).
7. Campbell, Campbell, and Eby, J. Am. Chem. Soc., 60, 2882 (1938).
8. Dupont, Bull, Soc. Chim (4), 15, 604 (1914).
9. Froming and Hennion, J. Am. Chem. Soc., 62, 653 (1940).
10. Gilman, Org. Chem., 2nd Ed., Chap. 7, p 672 (Wiley, 1943).
11. Grignard and Tcheoufaki, Bec. trav. chim., 48, 901 (1929).
12. Griner, Ann. Chim., 26, 359 (1892).
13. Helibron, Johnson, Jones and Spinks, J. Chem. Soc., 1942, 731.
14. Hurd and Cohen, J. Am. Chem. Soc., 53, 1068 (1931).
15. Johnson, H. W., Organic Seminar Abstracts, Univ. of Ill., May 5, 1943.
16. Jones and McCombie, J. Chem. Soc., 1942, 733.
17. Krafft and Heizmann, Ber., 33, 3590 (1900).
18. Kroeger and Nieuwland, J. Am. Chem. Soc., 58, 1861 (1936).
19. Liang, Bull. Soc. Chim. (4), 53, 44 (1933).
20. Moureu, Ibid (4), 31, 151 (1905).
21. Moureu and Brachin, ibid, 31, 170 (1904).
22. Moureu and Brachin, ibid, 31, 343 (1904).
23. Moureu and Brachin, ibid, 33, 131 (1905).
24. Moureu and Brachin, ibid, 33, 142 (1905).
25. Moureu and Brachin, ibid, 33, 147 (1905).
26. Moureu and Delange, ibid, 27, 378 (1902).
27. Moureu and Delange, ibid, 31, 1329 (1904).
28. Nef, Ann., 308, 276 (1899).
29. Nightingale and Wadsworth, J. Am. Chem. Soc., 67, 416 (1945).
30. Petrov, J. Gen. Chem. (U.S.S.R.) 10, 1682 (1940); C.A., 35, 3593 (1941).
31. Simonis and Lear, Ber., 59, 2903 (1926).
32. Tiffeneau and Deux, Compt. rend., 213, 753 (1941).
33. Tiffeneau and Deux, ibid, 214, 892 (1942).
34. Weygand, Bauer, and Heynemann, Ann., 459, 123 (1927).
35. Worrall, J. Am. Chem. Soc., 60, 1266 (1938).

Reported by Allen C. Moore
October 18, 1946

THE ROLE OF STERIC HINDRANCE IN NUCLEOPHILIC SUBSTITUTIONS

Whitmore and coworkers have shown that neopentyl compounds are strikingly unreactive in certain cases. The iodide reacts only slowly with alcoholic KOH at 180°, and then the main product is neopentane (1). The alcohol does not yield the chloride when treated with PCl_5, $SOCl_2$, etc. Bartlett and Rosen (2), have stated that the inertness of the neopentyl compounds must be due to steric hindrance, since the effect is not transmitted through an unsaturated linkage (C≡C), as it should be if it were polar. They also said that the lack of reactivity is limited to S_N2 reactions. S_N2 (Substitution, Nucleophilic, 2nd order) is a well demonstrated reaction mechanism wherein a nucleophilic (electron donating) group; such as OH^-, X^-, RO^-, NH_3, etc; attacks the carbon atom on the side opposite the group being replaced. Bartlett's article contains a



photograph of a Stuart model of neopentyl chloride wherein it is easily seen that access to the rear of the alpha carbon atom is difficult.

Dostrovsky, Hughes, and Ingold (3,4) have extended this work quantitatively. They measured the rates of reaction of neopentyl and other primary alkyl bromides with sodium ethoxide in absolute ethanol (See Table I). Kinetic studies showed clearly that this was in all cases a second order reaction. This was verified, in the case of neopentyl bromide, by the fact that an unrearranged product, ethyl neopentyl ether was obtained. In reactions, such as those proceding by the S_N1 mechanism, where the positive neopentyl ion is an intermediate, rearranged products are always obtained. S_N1, 1st order nucleophilic substitution, is a mechanism wherein there is a rate controlling ionization followed by the rapid reaction of the alkyl anion formed. The reaction rates

e.g. $Me_3CCl \rightarrow Cl^- + Me_3C^+ \xrightarrow{H_2O} Me_3COH + H^+$

and $Me_3CCH_2X \rightarrow X^- + Me_3CCH_2^+ \xrightarrow{H_2O} Me_2C(OH)CH_2Me + H^+$

decrease in the order methyl > ethyl > n-propyl > isobutyl > neopentyl, but by far the largest jump is between isobutyl and neopentyl. It is very improbable that the substitution of an additional methyl group in the beta carbon atom would have so profound effect if a polar influence were responsible. Furthermore, if the effect were polar, it should be even more noticeable in reactions of the S_N1 type. Yet, as is later shown, the rate constants in this type of reaction are of the same order for all of the primary bromides.

In order to create conditions which would favor the S_N1 reaction more, the solvolysis rate was measured in a more weakly nucleophilic, stronger ionizing solvent, 50% aqueous ethanol. Here, as shown in Table I, all of the reaction rates are much smaller than with the ethoxide, except the neopentyl which is actually larger. This is explained by the fact that the neopentyl bromide is reacting by an S_N1 mechanism. This mechanism cannot be proved by a study of the kinetics, since even a second order reaction with the solvent would appear first order because the concentration of solvent does not change appreciably during the reaction. However, it was proved by the following facts. The rate of reaction of the neopentyl bromide was found to be unaffected by addition of alkali. The reaction gave rearranged products (tertiary amyl alcohol, ethyl tertiary amyl ether, and trimethyl ethylene.) Additional experiments showed that the reaction constant increases with increase of the percentage of water in the solvent at the same rate that it does for reactions which are known to be S_N1 in mechanism (several times the rate for S_N2 reactions.) Despite the change in environment, the other bromides were still found to react by a S_N2 mechanism. Isobutyl bromide, the most likely to react in the S_N1 manner, was found to react much more rapidly in the presence of small amounts of alkali.

The reaction of the alkyl bromides with silver nitrate in aqueous alcohol was next studied. This reaction is complex, but resembles the S_N1 reaction. Here, as shown, the rate for neopentyl bromide is even closer to the values for the other bromides.

The condition which has been found most conducive to the S_N1 mechanism is solvolysis in wet formic acid (5). It is seen in this case that all of the reaction rates are of the same order.

Table I

Comparitive reaction rates (Ethyl = 1)

Alkyl bromide	Methyl	Ethyl	n-Propyl	isobutyl	neopentyl
NaOEt in EtOH	17.6(2)	1(2)	0.28(2)	0.030(2)	0.0000042(2)
50% H_2O-EtOH	2.03(2)	1(2)	0.58(2)	0.080(2)	0.0064(1)
Ag in H_2O-EtOH	0.81	1	0.55	0.084	0.013(1)
Wet HCO_2H	0.64	1(1)	0.69(1)	---	0.57(1)

1. S_N1 reactions
2. S_N2 reactions

Other reactions are of doubtful or mixed mechanism.

Thus it is shown that the S_N2 reaction rates are greatly reduced for neopentyl halides, but that the S_N1 reaction rates are practically unaffected.

In Table II is shown the activation energies calculated for two S_N2 reactions from the Arrhenius equation, $k = Ae^{-E/RT}$

Table II

Energy of activation (E) in kg-cal.

	Methyl	Ethyl	isobutyl	neopentyl
NaOEt in EtOH	20.0	21.0	22.8	26.2
I^- in acetone*		19.0		25.0

*This reaction was also studied and found to be S_N2.

From this table it may be seen that steric hindrance causes an increase of about 6 kg-cal. in the activation energy of neopentyl S_N2 reactions.

A semi-quantitative theoretical study of the effect of steric hindrance in the S_N2 reaction was attempted. The reaction of bromide ion with alkyl bromide is chosen because of several simplifications it makes possible. However, sufficient calculation with iodide, chloride, etc., is made to show that data obtained for the bromide reaction will apply well to the reaction with most anions. The distance between the bromine and its neighboring atoms is calculated both in the original molecules and in the transition state. These distances are compared with the theoretically calculated touching distances. It was found that there is practically no steric strain in any original molecule, but in the transition state certain distances are found to be smaller than the touching distance. This difference is referred to as "compression". The values are shown in Table III.

Table III

Amount and number of compressions in various transition state models

				number of such compressions						
dist.	Model dist.	Touch. dist.	comp.	Me	Et	iso Pro	tert Bu	n Pro	iso Bu	neo Pentyl
H_α-Br	2.55	2.68	0.13	6	4	2	-	4	4	4
	2.78	3.01	0.23	-	2	4	6	2	-	2
C_β-Br	2.78	2.98	0.20	-	-	-	-	-	2	-
	2.43	3.01	0.58	-	2	4	6	2	-	-
H_β-Br	2.30	3.02	0.72	-	-	-	-	-	1	-
	3.41	3.09	None	-	-	-	-	2	-	-
C_γ-Br	2.88	3.34	0.46	-	-	-	-	-	2	-
	2.42	3.47	1.05	-	-	-	-	-	-	2
	2.99	2.95	None	-	-	-	-	2	-	-
H_γ-Br	2.71	3.05	0.34	-	-	-	-	-	4	-
	2.15	3.13	0.98	-	-	-	-	-	-	4

These amounts of compression are then expressed in terms of energy. The results are limiting values based on the assumption that there is no stretching or bending of bonds. The quantal calculations necessary to allow for bending have not been worked out, but when allowance is made for stretching, the lowered values listed are obtained as maximum additions to the activation energy due to steric hindrance (in kg-cal). Methyl 0.0, ethyl 0.7, isopropyl 1.4, tert, butyl 2.2, n-propyl 0.7, isobutyl 2.3, neopentyl 11.7.

When it is considered that these values would be modified considerably downward if corrections for bond bending could be made, it is thought that the value of 11.7 kg-cal obtained for neopentyl, for example, is not irreconcilable with the value of about 6 kg-cal found by experiment.

These results have modified some of Ingold's theories of reactions and mechanisms.

Bibliography

1. Whitmore, Wittle, and Popkin, J. Am. Chem. Soc., 61, 1586 (1939).
2. Bartlett and Rosen, J. Am. Chem. Soc., 64, 543 (1942).
3. Dostrovsky, and Hughes, J. Chem. Soc., 1946, 157, and five following articles.
4. Dostrovsky, Hughes, and Ingold, J. Chem. Soc., 1946, 173.
5. Bateman and Hughes, J. Chem. Soc., 1940, 945.

Reported by Jack Hine
October 25, 1946

SOME USES OF SELENIUM DIOXIDE IN ORGANIC CHEMISTRY

The use of selenium dioxide has constituted one of the more recent developments in the field of organic chemistry. A patent in 1931 by I. G. Farbenindustrie was the first reference to practical use of selenium dioxide as an oxidizing agent for organic molecules, and in 1932 a systematic study of the reactions which could be made to occur by use of this reagent was begun by Riley and his co-workers in England. The patent covered the oxidation of methyl side-chains on three polynuclear compounds to aldehyde or carboxyl groups, and the oxidation of one benzyl derivative to the corresponding benzoyl compound. The early work of Riley was concerned with oxidizing ketones, aldehydes, and unsaturated hydrocarbons to glyoxal derivatives. Some of his transformations were

acetone to methylglyoxal	60% yield
acetophenone to phenylglyoxal	50% "
acetaldehyde to glyoxal	90% "
butyraldehyde to ethylglyoxal	40% "
phenylacetaldehyde to phenylglyoxal	35% "
ethylene to glyoxal	82% "
propylene to methylglyoxal	19% "
acetylene to glyoxal	6% "

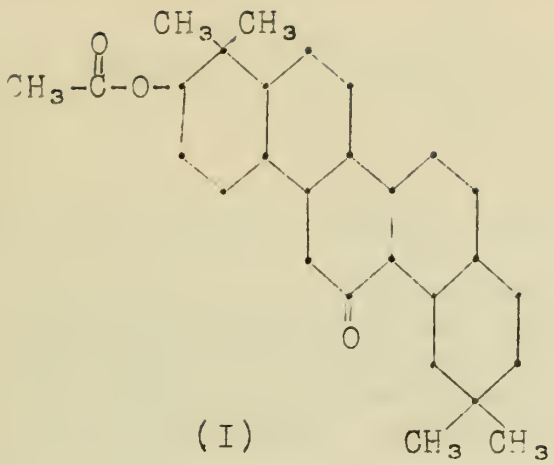
The features of the reaction were that it was selective for active methyl and methylene groups, and that the functional group was not destroyed in the oxidation.

Since these original investigations, selenium dioxide has been used for a great many other oxidation reactions, including dehydrogenation, and in some instances for catalysis and for coupling, often in sensitive molecules which can stand only mild treatment.

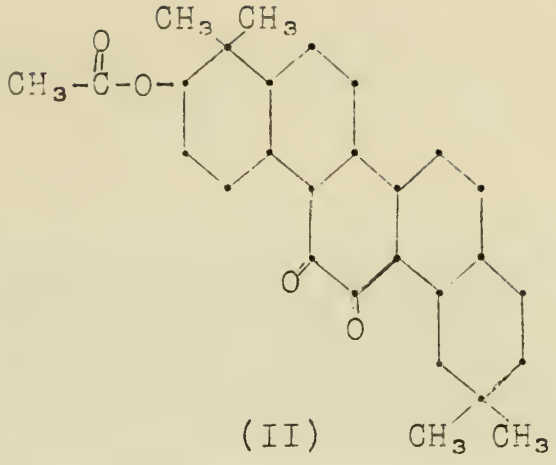
1. Reaction with saturated compounds.--In general saturated hydrocarbons, alcohols, ethers, acids, esters, and most halogenated compounds are not attacked by selenium dioxide at ordinary temperatures, but may be oxidized at higher temperatures. Alcohols will form selenite esters of the form $ROSeO_2H$ at ordinary temperatures and $(RO)_2SeO$ at higher temperatures, which accounts for the solubility of SeO_2 in alcohols. Consequently alcohols are often used as solvent media for selenium dioxide oxidations.

Ethane is oxidized to glyoxal, acetic acid, and CO_2, but the reaction is not very useful. Acetic and formic acids do not react with selenium dioxide, so acetic acid and acetic anhydride are useful solvents for these reactions. Propionic acid can be oxidized to pyruvic acid, but only in 2% yields. Fatty acids are decarboxylated then desaturated by selenium dioxide; lauric acid, for example, gives undecene.

Some useful reactions of saturated compounds can be found in the terpene field. The acetate of β-amyranonol (I) can be oxidized to the acetate of β-amyranedionol (II) and a crystalline product is obtained, while with other oxidizing agents the product is amorphous.



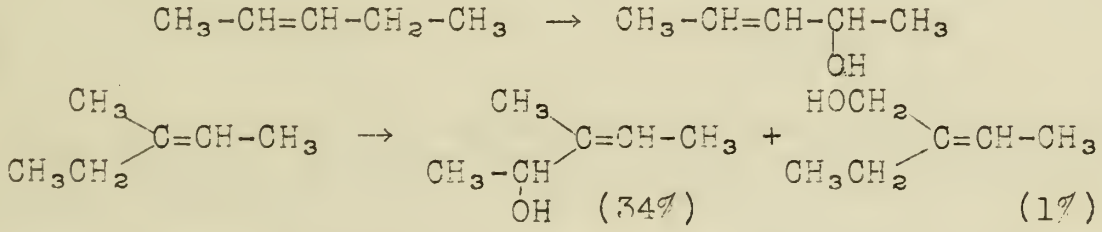
(I)



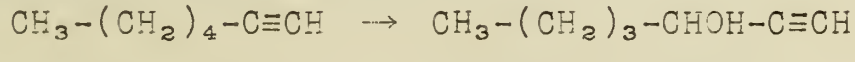
(II)

Borneol and isoborneol can both be oxidized to camphorquinone in 60% yields.

2. Reaction with unsaturated compounds.--Many of the more recent developments of selenium dioxide reactions have been with unsaturated compounds. Unsaturated alcohols can be prepared by oxidation of olefins. The point of attack is at the carbon α to the double bond. The ease of oxidation decreases in the order $CH_2 > CH_3 > CH$ in general, although a tendency to avoid substituted carbon atoms also enters the picture in some cases. A few typical examples are,

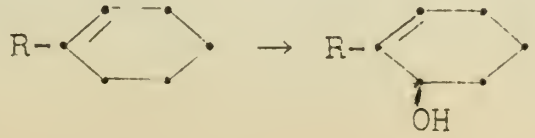


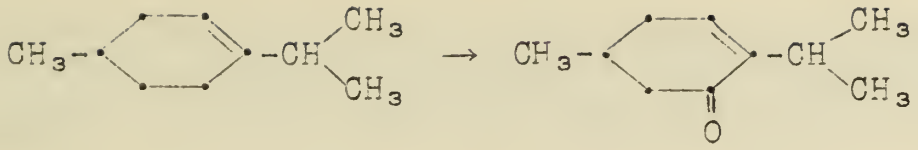
The oxidation usually stops at the alcohol stage, although by using proper conditions it can be made to proceed to the aldehyde or ketone in some instances. Acetylenes respond to selenium dioxide just like olefins do.



1-heptyne 1-heptyne-3-ol

In the hydroaromatic and aromatic series, oxidation more often produces the carbonyl compound, although some oxidations to alcohols are recorded. Guillemonat (3), who has done a great deal of work on uses of selenium dioxide, observed that in an unsaturated alicyclic hydrocarbon with substituted ethylenic carbon atoms, oxidation occurs in the α-position to the most substituted carbon atom and in the cycle if possible.

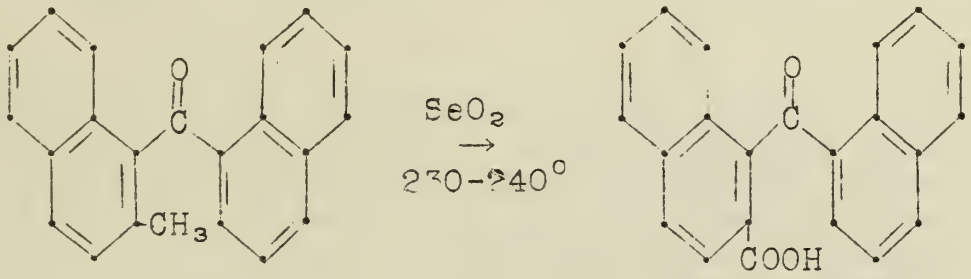




Some other typical examples are

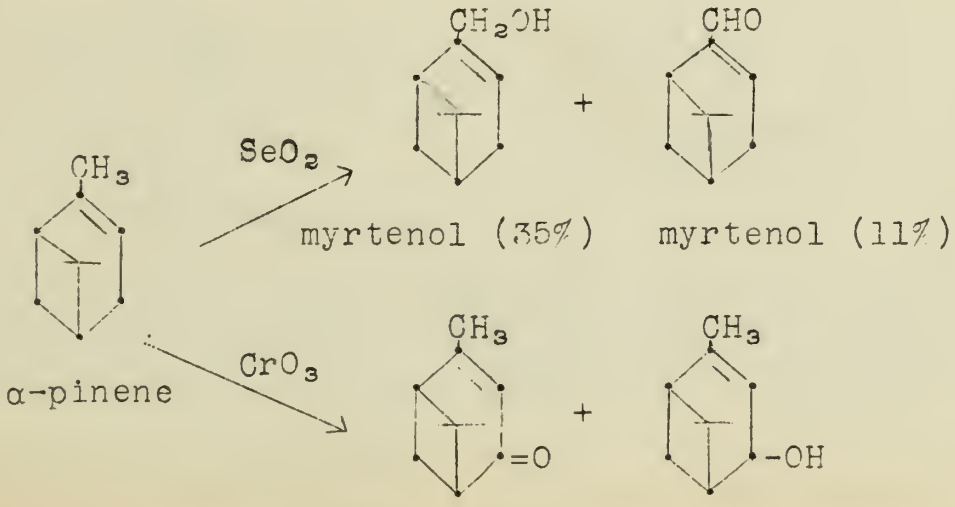
anthracene is oxidized to anthraquinone in 75% yields
diphenylmethane produces benzophenone in 87% yields
fluorene in transformed to fluorenone in 55% yields
phenanthrene gives phenanthraquinone in only 5% yeilds
2- and 6-methyl benzanthrenes gives the corresponding aldehydes

Cook (4) prepared the only one of the five dibenzanthracenes which was unknown, the 1,2,7,8-dibenzanthracene, by selenium dioxide oxidation of 2-methyl-1,1'-dinaphthyl ketone to the corresponding 2-carboxylic acid and then closing the ring and reducing; other oxidizing agents in this case gave no useful products.



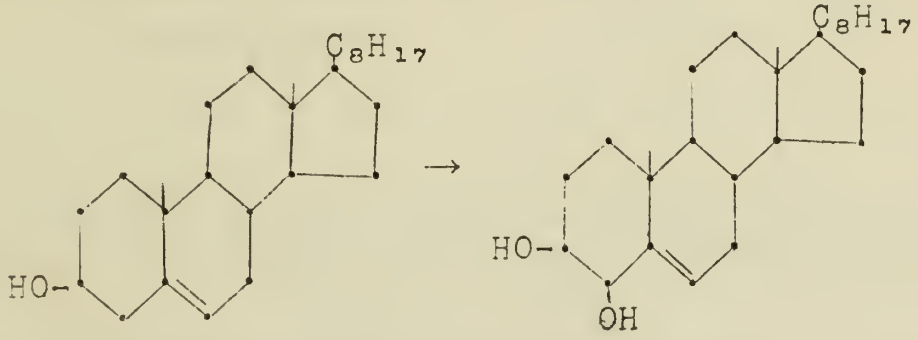
If a group is partly oxidized, further oxidation is facilitated. For example, toluene gives benzoic acid in only 27% yield with SeO_2, but benzyl alcohol gives benzaldehyde in 95% yields.

Nitrotoluenes are inert to selenium dioxide, and in general phenols, cresols, aminophenols, amines, and phenol ethers give only tars on oxidation with this reagent. Bicyclic terpenes react readily but usually give mixtures. α-Pinene gives myrtenol and myrtenal, and furnishes a beautiful contrast to chromic acid oxidation.



β-Pinene gives pinocarvone, pinocarveol, and carvopinone, the relative amounts depending on purity of starting material, temperature, solvent, relative amount of SeO_2 used, and to some extent, experimenter.

Of course some of the most useful applications of these reactions have been in synthesis of sterols, bile acids, hormones, and other natural products where mild oxidation is necessary. One example is the oxidation of cholesterol to 4-hydroxycholesterol. Many other examples of uses in these fields are known. Ruzicka has done distinguished work along these lines.

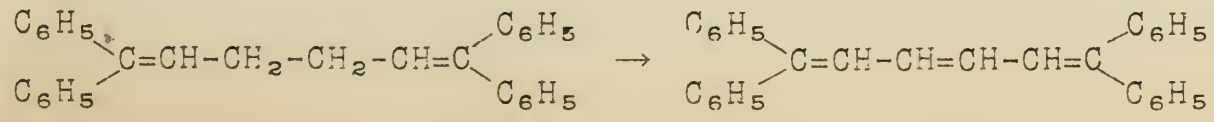


Oxidation in the heterocyclic ring systems is very similar to that in the carbocyclic ones. α-Methylpyridine can be oxidized to either to the aldehyde or the carboxylic acid, depending on the conditions used. Quinaldine gives principally the aldehyde. 2-Ethyl-3-methylquinoline is oxidized to the 3-methyl-2-quinoline-carboxylic acid, oddly. Methyl side-chains on pyrimidine, quinazoline, and benzimidazole nuclei all give aldehydes, for example,

2-methylbenzimidazole

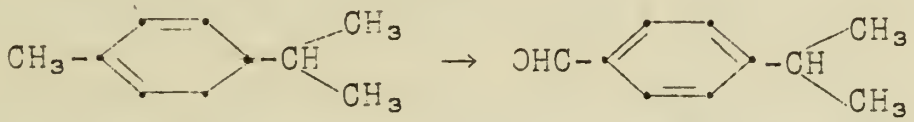
2-methylquinazolone

Dehydrogenation is also a common and an important reaction produced by selenium dioxide. Well known examples are the preparations of polyenes, as in the conversion of 1,1,6,6-tetraphenyl-1,5-hexadiene to the corresponding hexatriene. Dibenzyl is converted



to stilbene at 300°, and on subsequent oxidation goes on to benzil, the latter step going in 85% yields. Tolane also gives benzil, but in only 35% yields, the reaction going at 280°. Benzylcamphor gives benzilidenecamphor in quantitative yields.

A few cases are known where oxidation and dehydrogenation occur together. An example is,

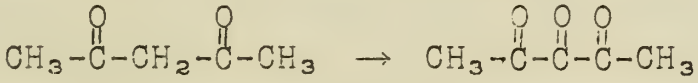


α-phellandrene cuminaldehyde

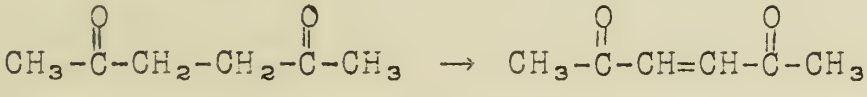
Similarly, thymol gives piperitone on selenium dioxide treatment.

Of all the examples of catalytic action of SeO_2, one stands out as spectacular. If cyclohexene is oxidized with H_2O_2 in the presence of selenium dioxide, pure trans-cyclohexanediol results.

3. Reaction with aldehydes and ketones.--The fact that selenium dioxide has a specific oxidizing action on active methyl and methylene groups has already been pointed out. These reactions usually go in high yields, and are especially useful for preparing polyketones. 1,3-Diketones are oxidized to triketones, for example, acetylacetone gives dimethyl triketone,

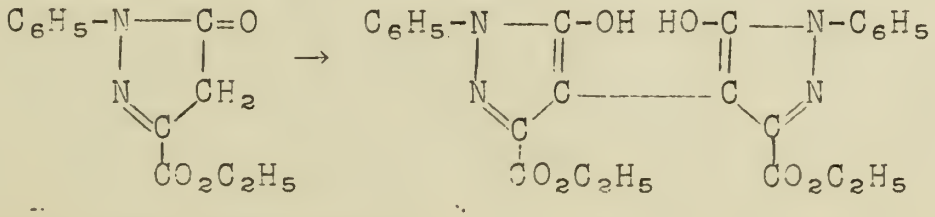


1,4-Diketones undergo desaturation, for example, acetonylacetone gives diacetylethylene,

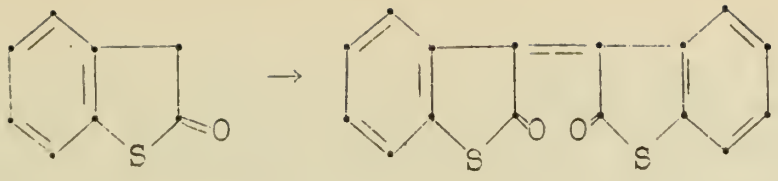


These reactions are very useful and quite general.

4. Some condensation reactions.--A few cases of attempted oxidation which should have gone well resulted in condensation of two molecules. The reaction is not general, nor has it been studied and characterized yet, but the examples on record are



5-oxy-1-phenyl-pyrazoline-
2-carboxylic ester



2-hydroxythionaphthene isothioindigo (35% yield)

5. Mechanism of the reaction.--A good deal of work has been done on the mechanism of selenium dioxide reactions by Guillemonat (3) and by Emeleus and Riley (5). There seems to be little doubt that organoselenium intermediates form which eleminate Se under mild conditions leaving the oxidation products. Many intermediates have been isolated. Emeleus and Riley have likened oxidation with SeO_2 to peroxidation or auto-oxidation.

The mechanism proposed for oxidation of alcohols is,

$$2RCH_2OH + SeO_2 \rightarrow (RCH_2)_2SeO_3 + H_2O$$

$$(RCH_2)_2SeO_3 \rightarrow 2RCHO + Se + H_2O$$

The selenium can be recovered and reused.

The mechanism for oxidation of hydrocarbons to alcohols proposed is,

$$\begin{matrix} RCH_2H \\ O{=}Se{=}O \\ RCH_2H \end{matrix} \quad \begin{matrix} HCH_2R \\ \\ HCH_2R \end{matrix} \rightarrow (RCH_2)_4Se \xrightarrow{H_2O} RCH_2OH + RCH_3 + RCH_2-Se-CH_2R$$

$$\underline{Se} + RCH_3 + RCH_2OH \leftarrow RCH_2-Se-CH_2R$$

and the mechanism for dehydrogenation proposed is,

$$CH_3-CH=\underset{\displaystyle CH_3}{C}-CH_2-Se-CH_2-\underset{\displaystyle CH_3}{C}=CH-CH_3 \rightarrow CH_2=CH-\underset{\displaystyle CH_3}{C}=CH_2 + CH_3-\underset{\displaystyle CH_3}{C}=CH-CH_3$$

The yields in general are consistent with these mechanisms as well as many other factors.

6. Technique and generalizations.--Selenium dioxide functions as a mild oxidizing agent over a wide range of temperatures. At ordinary temperatures specific oxidation takes place at methyl and methylene groups which are activated by being adjacent to double bonds, carbonyl groups, benzene nuclei, or nitrogen atoms in heterocyclic rings. Some of these oxidations can be carried out at room temperature with the aid of sunlight or ultraviolet light. Yields and types of oxidation products obtained are affected by the solvent used, the quantities of reagents used, and the temperature. In glacial acetic acid, acetic anhydride, and sometimes in alcohol solvents, the reaction generally proceeds only as far as

the alcohol stage. The effect of temperature is shown by the work of Campbell and Harris (6) who found that when $\Delta^{9,10}$-octalin is oxidized with selenium dioxide at 5° it gives $\Delta^{9,10}$-octal-1-ol, at 30° it gives $\Delta^{9,10}$-octalin-1,5-diol, and at 120° the product is hexahydronaphthalenediol-1,5.

Although SeO_2 is often used as a dehydrogenating agent, it rarely splits the C-C bond. For catalytic action, SeO_2 is often used in sulfuric acid solvent (recall Kjeldahl nitrogen determination).

The reactions with SeO_2 are fairly predictable, usually controllable, well adapted to laboratory procedures, and usually proceed without causing any disruption or rearrangement in the molecule. This reagent effects many mild oxidations impossible with ordinary oxidizing agents.

A rather complete table of general organic molecules which have been subjected to selenium dioxide oxidation and the products which were isolated, along with references to original work in each case, is given on pp. 258-283 of a review article by Waitkins and Clark (2).

Bibliography

1. Vené, Bull, soc. chim. (France), 12, 506 (1945).
2. Waitkins and Clark, Chem. Rev., 36, 235 (1945).
3. Guillemonat, Ann. Chim., 11, 143 (1939).
4. Cook, J. Chem. Soc., 1932, 1472.
5. Emeleus and Riley, Proc. Roy. Soc. (London), A140, 378 (1933).
6. Campbell and Harris, Jour. Am. Chem. Soc., 63, 2721 (1941).
7. Yokoyama, Jour. Chem. Soc. Japan, 59, 271 (1938).

Reported by K. V. Beck
October 25, 1946

THIONES AND THIALS

Part I - Preparation and Properties

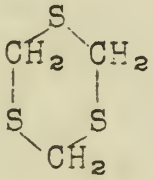
Thiones and thials are compounds of the structure $R\overset{S}{\overset{\|}{C}}R'$, where R and R' may be H, alkyl, or aryl groups. Also included in the discussion are compounds of the formula $(RCSR')_n$, where n = 2 or 3, and of the formula $HS(RCSR')_xH$, where x is any number, usually greater than 3.

Preparation.--The most useful method of preparation of thials and thiones is by the action of hydrogen sulfide on a solution of the aldehyde or ketone, usually in the presence of acid. As reported in Organic Syntheses (1), this reaction yields 92-94 per cent of trithioformaldehyde.

A possible mechanism for the reaction (2) involves first the addition of H_2S to formaldehyde. Three molecules of this addition

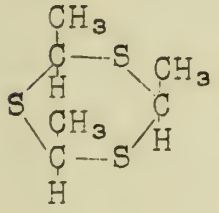
$$CH_2O + H_2S \rightarrow CH_2\begin{matrix}SH\\OH\end{matrix}$$

product then react, with loss of water to give the trimer

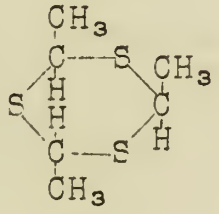


or they may polymerize to give $HSCH_2SCH_2SCH_2OH$ or larger molecules. Alkyl thials probably do not exist in the monomeric form (3a).

Acetaldehyde reacts similarly to give trithioacetaldehyde. Two isomers (cis-trans) of this compound are known.



and

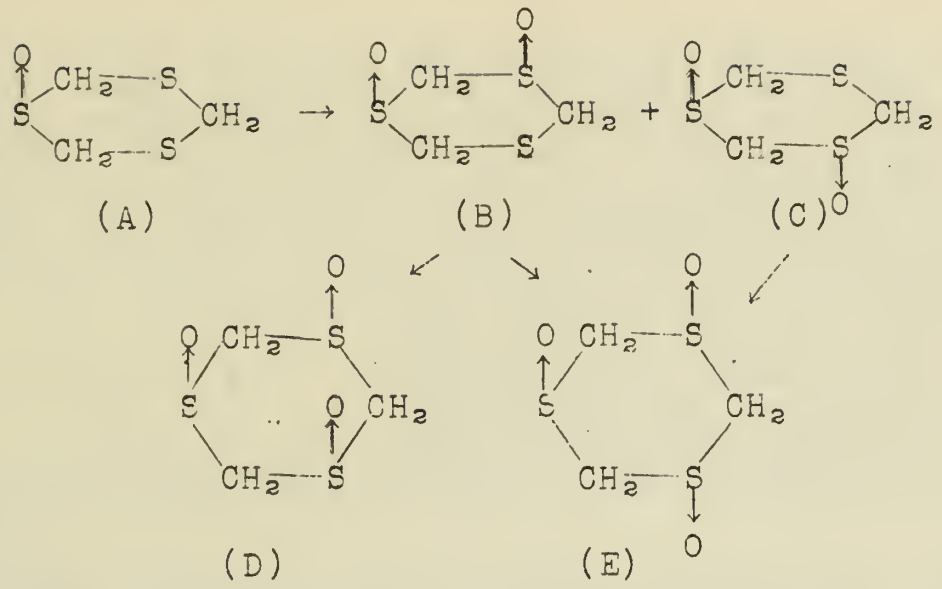


Aryl thials and alkyl- and alkoxy-substituted aryl thials have been prepared in the same way. Similarly, thiones are prepared by the action of hydrogen sulfide on ketones. Thiones trimerize readily also.

Other methods of preparing thials include action of sodium thiosulfate on aldehydes, reaction of thioacetoacetic esters with aldehydes, and reaction of sulfides with alkyl halides.

For thiones, special methods of prepartion include action of phosphorus sulfides on ketones and reaction of vinyl halides with metal sulfides.

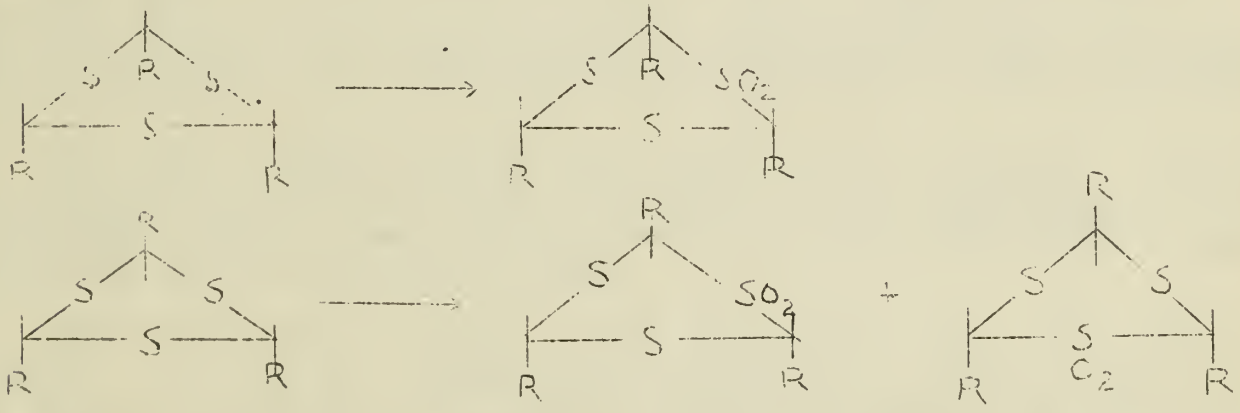
Trithioformaldehyde has been proved to exist in a planar ring structure (4). All of the sulfoxides which would theoretically exist for such a structure have been isolated. Only one monoxide



(A) (B) (C) (D) (E)

A, is known, which forms two different disulfoxides, B and C. C yields only one trisulfoxide, E, so the trans structure was assigned to C. B yields two trisulfoxides, one identical with E, and a different one, D. This indicates that B has the cis configuration. A nonplanar structure would require more isomers.

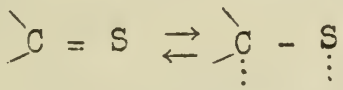
Trithioacetaldehyde exists in cis and trans forms, as stated earlier. The production of one or the other isomer can be favored by varying the conditions under which the preparation is carried out; the less stable α-form (m.p. 101°C) can be converted into the β-form (m.p. 125°C) by various means. The proof of structure of this compound has been on the basis of the monosulfones (5). The α-form yields one monosulfone, while the β-form yields two. All



three monosulfones are different. On this basis, the lower melting, more soluble α-isomer has been assigned the cis-trans structure, while the higher melting, less soluble β-form is called cis. Since this is contrary to the usual behavior of cis and trans isomers (3b), the question of structure is still open to some doubt.

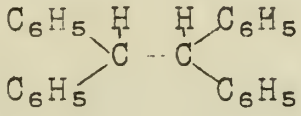
Physical properties.--Virtually all the monomeric thiones are colored (3c). Absorption curves of some thiones have been measured. Several thiones show a band at 5900 Å (6) and other characteristic bands have been observed in various compounds. In

the series C=NH, C=O, C=S the extinction increases and the absorption bands shift toward the red in that order (7,8). On the basis of optical properties it has been proposed that thiones exist in a free-radical form to a small extent. The absorption curves show a difference in the structure of the carbonyl and thiocarbonyl group (9). The behavior and color characteristics of thiones indicate the possibility that they exist in a thione-free-radical tautomerism. Facts which bear this out are the similarity of the

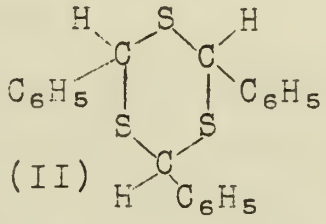


color changes of diaryl ketones and hexarylethanes when methoxy or dimethylamino groups are introduced, and the similar chemical reactions of diaryl thiones and triarylmethyls (such as the formation of unstable peroxides in air.)

Further evidence of free radical formation is found in the comparison of the dissociation tendencies of the polymeric thiones and the corresponding members of the ethane series (10). Tetraphenylethane (I) and 2,4,6-triphenyltrithiane (II) are stable, but replacing the hydrogens with phenyl groups greatly increases the tendency to dissociate.



(I)



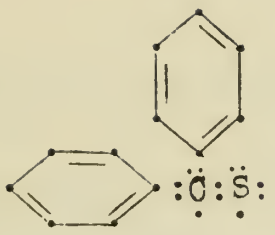
(II)

The dipole moment of the C=S group is about 0.5×10^{-18} greater than that of the C=O group. It has been proposed that this is evidence of a difference in structure of the two groups, since a smaller moment would be expected for the C=S group (9).

The bond energy for the C=O group is 152 kg.-cal., and that for the C=S group is 103 kg.-cal. (11). This difference, indicating a much weaker bond, is in accord with the free-radical type of structure in the C=S group (3d).

The interatomic distance also agrees with the free-radical concept. Use of the interatomic distances of Pauling (11) gives the value 1.61 Å for the carbon-to-sulfur distance in C=S, and 1.26 Å for the carbon-to-oxygen distance in C=O. (These figures were not determined on thiones.)

Recently, Lewis and Kasha (12,13) have made some interesting calculations based on phosphorescence and absorption of compounds in the triplet or biradical state. A typical example of this biradical state would be the free radical of thiobenzophenone.



Thiobenzephenone was used to demonstrate the identity of the phosphorescent and the triplet states. The triplet-state energy (E'_t = kg.-cal.) for the thiobenzophenone was calculated from both phosphorescence and absorption-spectrum data. It was shown that the abnormal colors of the monomeric thiones are due to absorption from the singlet to the triplet state.

The tendency of thiones to dimerize or trimerize was also discussed (13). If the energy of association is represented by E_{Dim}, the dimer is thermodynamically stable when $E_{Dim} > 2E_t$, where E_t stands for the triplet-state energy. Therefore, in all cases where E_t is small, dimerization might be expected. This does not hold when E_{Dim} is also small, owing to steric hindrance or other effects, as in the case of di-tert-butyl thione. Similar conditions apply to the case of trimerization also.

Bibliography

1. Bost, R. W., and Constable, E. W., Org. Syntheses 16, 81 (1936).
2. Baumann, E., Ber. 23, 60 (1890).
3. (a) Campaigne, E., Chem. Reviews 39, 4 (1946); (b) loc. cit., p. 45; (c) loc. cit., p. 46; (d) loc. cit., p. 49.
4. Bell, E. V., and Bennett, G. M., J. Chem. Soc., 1929, 15.
5. Chattaway, F. D., and Kellett, E. G., J. Chem. Soc., 1930, 1352.
6. Bost, R. W., and Cosby, B. O., J. Am. Chem. Soc., 57, 1404 (1935).
7. Burawoy, A., Ber., 63, 3155 (1930).
8. Burawoy, A., Ber., 64, 462 (1931).
9. Donle, H. L., and Volkert, G., Z. physik, Chem. B8, 64 (1930).
10. Schönberg, A., Ber., 62B, 462 (1931).
11. Pauling, L., "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York (1945).
12. Lewis, G. N., and Kasha, M., J. Am. Chem. Soc., 66, 2113 (1944).
13. Lewis, G. N., and Kasha, M., J. Am. Chem. Soc., 67, 998 (1945).

Reported by T. M. Vial
November 1, 1946

Part II - β-Thioketonic Esters

Extensive investigations of β-thioketo esters were made by Mitra, upon whose work the following report is based.

When ethyl β-chlorocrotonate was treated with potassium bisulfide in alcohol, a 30% yield of ethyl thioacetoacetate (II) and a considerable amount of ethyl β-dicrotonyl sulfide (I) resulted.

$$CH_3\overset{Cl}{C}=CHCO_2C_2H_5 \xrightarrow{KSH} CH_3-\underset{S}{C}=CH_2CO_2C_2H_5 + CH_3-\underset{S}{C}=CH_2CO_2C_2H_5 \quad (I)$$

$$CH_3-\overset{SH}{C}=CHCO_2C_2H_5 \rightleftarrows CH_3-\overset{S}{C}-CH_2CO_2C_2H_5 \quad (II)$$

Thioacetoacetic ester reacted with phenylhydrazine to give phenylmethylpyrazolone in 60% yield. It also reacted with hydroxylamine with evolution of hydrogen sulfide. The presence of the thiol group was proven by decolorization of an alcoholic solution of iodine and by formation of the lead salt.

Ethyl thioacetoacetate and ethyl thioacetonedicarboxylate have been prepared in 85% and 75% yields, respectively, by passing hydrogen sulfide into an alcoholic solution of the corresponding β-keto esters saturated with hydrogen chloride. The thioketonic esters were purified by decomposition of an alcoholic suspension of their lead salts with hydrogen sulfide.

Thioacetoacetic ester can be alkylated by the action of alkyl halide on its sodium derivative in benzene. Thioacetoacetic ester differs, however, from acetoacetic ester in that the S-ether is obtained rather than the C-alkylated product.

On treatment of the β-alkylmercapto compound with phenyl hydrazine under ordinary conditions, no hydrogen sulfide is evolved--showing the absence of a thioketonic group. If the reaction is carried out at elevated temperatures, the corresponding mercaptan and dehydropyrazolone result.

The S-ethers of the β-thioketonic esters do not react further with sodium. The dialkyl derivatives analagous to those of acetoacetic ester could not be obtained directly and the effect of the thiocarbonyl group on the second hydrogen atom of the reactive methylene group could not be studied.

The C-alkyl derivative of thioacetoacetic ester can be synthesized from ethyl α-ethylacetoacetate by the hydrogen sulfide-hydrogen chloride method. The S-ether is then prepared in the usual manner.

Mitra also studied the equilibrium reaction

$$CH_3\overset{SH}{C}=CRCO_2C_2H_5 \rightleftarrows CH_3\overset{S}{\overset{\|}{C}}-CHRCO_2C_2H_5$$

and estimated the per cent of thiol at various temperatures.

Bromination for keto-enol estimation could not be used in the case of thioketonic esters because of side reactions other than the addition of bromine at the double bond. These side reactions might be oxidation of thiol to disulfide, oxidation to sulfone, addition of bromine to the sulfide, or reaction with a hydrogen atom of the active methylene group.

The method of oxidizing the thiol to the disulfide by means of an alcoholic solution of iodine was employed. The procedure adopted was to maintain the β-thioketonic ester in alcohol in a thermostat at the required temperature for six hours, then quickly transfer it to an alcoholic solution of iodine at -7° and titrate the excess iodine with sodium thiosulfate solution. The results are summarized in the following table.

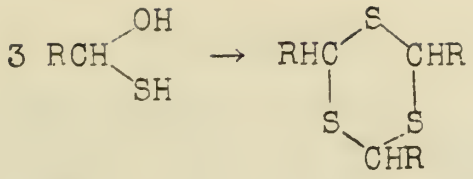
$CH_3CSCHRCO_2C_2H_5$	% thiol in equilibrium 30°	40°	60°
1. R = H	41	--	38.7
2. R = CH_3	62.8	61.9	60.0
3. R = $CH_2CH(CH_3)_2$	--	--	64.4
4. R = $CO_2C_2H_5$	61.1	--	58.5

It is evident that there is a shift toward the thione phase as the temperature is increased and that substitution on the carbon atom increases the thiol phase.

Mitra found that β-thioketonic esters condensed with aldehydes in the presence of acids and a trace of moisture to form trithioaldehydes and the ketonic esters. The fact that the reaction could not be carried out in a perfectly anhydrous medium suggested that aldehydes first form an unstable hydroxy sulfides (III) with β-thioketonic esters in the thiol phase and upon hydrolysis yielded the hydroxymercaptans (IV) which lost water intramolecularly to form stable trithio derivatives (V).

$$CH_3\overset{SH}{C}=CHCO_2C_2H_5 \xrightarrow{RCHO} \left[CH_3\overset{SCHR}{\overset{|}{C}}(OH)=CHCO_2C_2H_5\right] \xrightarrow{H_2O} RCH(OH)(SH)$$

III IV



V

Several aryl thials and one alkyl thial, trithioformaldehyde, were prepared in this manner. The general procedure involved dissolving the β-thioketonic ester in alcohol saturated with hydrogen chloride at 0°. The aldehyde together with a few drops of water was next added to the mixture which was kept at 100° for a short time and left overnight. The products were identified with those obtained by the reaction of aldehyde with hydrogen sulfide in an alcohol solution saturated with hydrogen chloride.

In support of this mechanism, Mitra was able to prepare ethyl β-methoxymethylmercaptocrotonate (which is the methyl ether of III when R equals hydrogen) by the action of chloromethyl ether and ethyl sodiothioacetoacetate in benzene. Hydrolysis of the reaction product with concentrated hydrobromic acid at room temperature gave trithioformaldehyde.

By using ethyl α-methylthioacetoacetate, ethyl α-isobutylthioacetoacetate, diethyl thioacetonedicarboxylate and diethyl thioacetylmalonate as β-thioketonic esters, benzaldehyde, formaldehyde anisaldehyde and vanillin formed the corresponding β-trithioaldehydes.

Aldehydes and β-thioketonic esters also reacted in alkaline media giving trithials. Thioacetoacetic ester and benzaldehyde condensed in piperidine to an oil which solidified upon standing for twenty-four hours. Molecular weight determinations and analyses indicated that this compound was a polymer $(C_6H_5CHS)_7$, (m.p. 82-83°). When the polymer was treated with piperidine and chloroform followed by benzoyl chloride, β-trithiobenzaldehyde resulted (m.p. 226°). Treatment of anisaldehyde in the same manner gave a solid, melting at 73-75°, which proved to be $(CH_3OC_6H_4CHS)_{11}$. These various polythials were depolymerized in basic media since they gave phenylhydrazones with phenylhydrazine alone or in pyridine.

Monomeric thioacetophenone and thiobenzophenone have been prepared from the corresponding ketones and thioacetoacetic ester and hydrogen chloride. The former is a dark violet oil boiling at 110° at 20 mm. pressure, and the latter a blue oil, boiling at 155° and 10 mm.

With few exceptions monomeric thiones are highly colored compounds.

Bibliography

1. Campaigne, Chem. Rev., 39, 1 (1946).
2. Mitra, J. Indian Chem. Soc., 8, 471 (1931).
3. Mitra, J. Indian Chem. Soc., 9, 633 (1932).
4. Mitra, J. Indian Chem. Soc., 10, 71 (1933).
5. Ray, Mitra and Ghosh, J. Indian Chem. Soc., 10, 75 (1933).
6. Mitra, J. Indian Chem. Soc., 10, 491 (1933).
7. Mitra, J. Indian Chem. Soc., 15, 129 (1938).
8. Mitra, J. Indian Chem. Soc., 15, 205 (1938).

Reported by A. J. Speziale
November 1, 1946

REDUCTIONS WITH NICKEL-ALUMINUM ALLOY IN AQUEOUS ALKALI

I. Carbonyl compounds.--Unlike certain other methods for the reduction of carbonyl compounds this method is not specific. The type of reduction product is dependent upon the following factors.

1. Structure of carbonyl compound
   $C_6H_5COR \rightarrow$ hydrocarbon
   R = H, alkyl, aryl
   $C_6H_5(CH_2)_xCOR' \rightarrow$ Carbinol
   R' = H, or alkyl
2. Solubility of carbonyl compound in alkali.
3. Effect of solvent.

II. Displacement of groups by hydrogen.--When treated with nickel-aluminum alloy in aqueous alkali halogen and sulfonic acid groups are displaced by hydrogen, the displacement of these groups being apparently independent of their number, their position, or the presence of other groups.

In disubstituted benzene derivatives the alkoxyl groups can be displaced by hydrogen, the displacement being dependent upon the nature and position of the other substituent.

With the introduction of a third substituent in the benzene ring the displacement of alkoxyl leads to complications.

III. The carbon-carbon double bond.--In all compounds containing aliphatic chain double bonds, and a chain double bond in conjugation with an alicyclic double bond the reduction proceeds smoothly and in good yields. An anomolous behavior is observed in reduction of isolated ring double bonds.

IV. Rupture of the methylenedioxyl bridge.--Methylenedioxybenzene and several of its derivatives substituted in the 4-position, on reduction with nickel-aluminum alloy and aqueous alkali, are converted to the m-hydroxy compounds in good yields; the conversion being independent of the type of substituent present.

Bibliography

Whitman, Wintersteiner, Schwenk, J. Biol. Chem., 118, 789 (1937).
Papa, Schwenk, Whitman, J. Org. Chem., 7, 587 (1942).
Schwenk, Papa, Ginsberg, Ind. Eng. Chem., Anal. Ed., 15, 576 (1943).
Schwenk, Papa, Whitman, Ginsberg, J. Org. Chem., 9, 1 (1944);
ibid., 9, 175 (1944).
Schwenk and Papa, ibid., 10, 232 (1945).

Reported by C. R. Morgan
November 8, 1946

THE WILLGERODT REACTION

The Willgerodt reaction has in the past referred to the conversion of an aralkyl ketone to an amide with the same number of carbon atoms, but recent publications indicate that it is effective as well with aliphatic ketones. The original process involved reaction of the ketone with an aqueous solution of ammonium polysulfide at a temperature in the range of 200° to 225° C. in a sealed tube. The reaction may be expressed by the following equation

$$ArC(=O)(CH_2)_nCH_3 \xrightarrow[H_2O]{(NH_4)_2S_x} ArCH_2(CH_2)_nCONH_2.$$

The Kindler modification which was introduced in the 1920's consists of heating the ketone with sulfur and a dry amine instead of aqueous ammonium polysulfide. A thioamide is formed as the principal product and hydrolysis with acid or alkali gives the carboxylic acid (1, 2, 3).

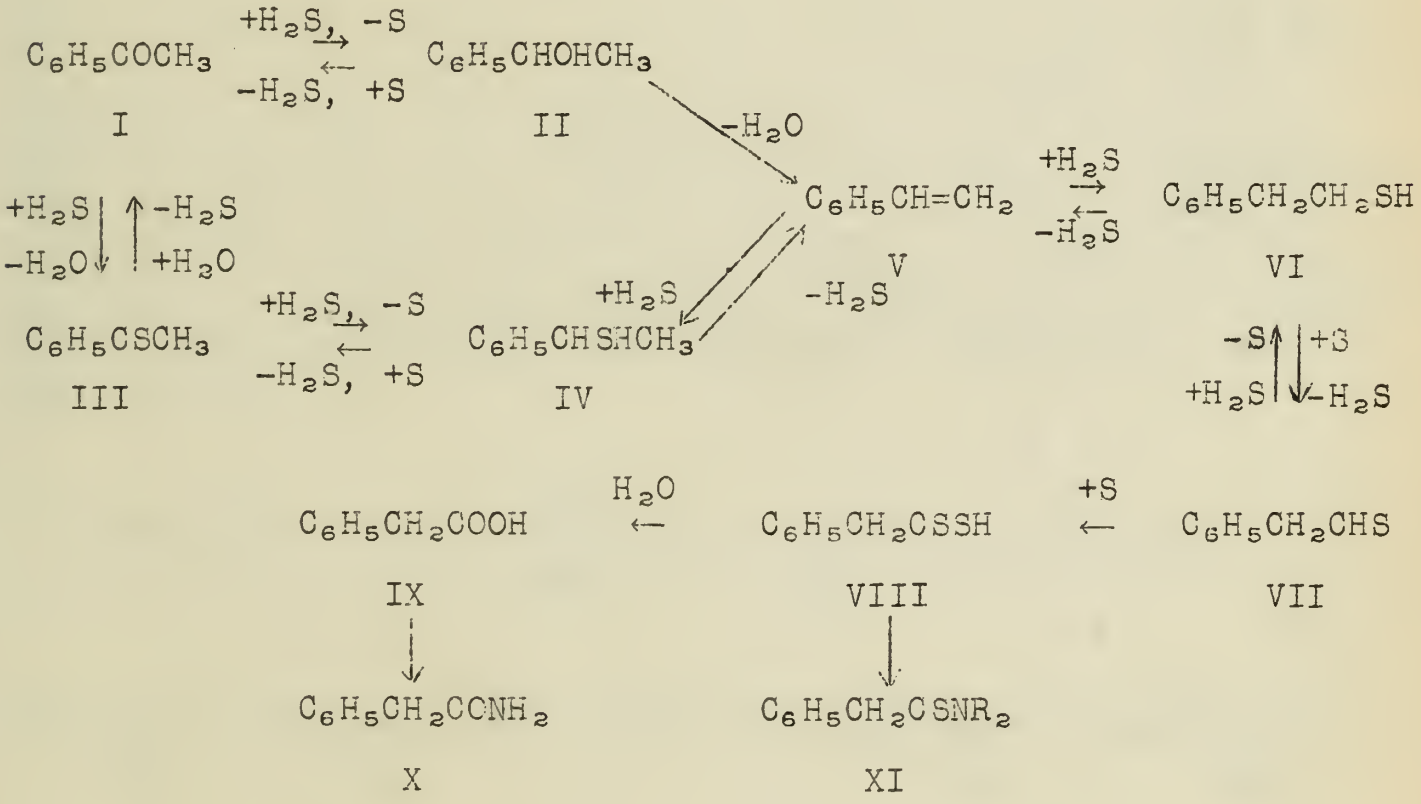
In 1945 Cavalieri, Pattison and Carmack (4) announced their successful application of the reaction to purely aliphatic and to alicyclic-aliphatic ketones which thus affords a new approach to the synthesis of branched or straight chain fatty acids. King and McMillan (5) subjected phenylacetone to the Willgerodt reaction and obtained β-phenylpropionamide showing that it was not necessary for the carbonyl group to be adjacent to the aromatic ring in the aromatic aliphatic ketones. In addition they showed that methylphenylcarbinol and its dehydration product styrene gave phenylacetamide in approximately the same yield as did acetophenone. Carmack and DeTar also applied the reaction to olefins and as well to acetylenes.

Mechanism.--The following facts must be explained in any proposed mechanism: (1) ketones, alcohols, olefins, acetylenes and aldehydes all react similarly; (2) no rearrangement occurs; (3) an aralkyl hydrocarbon is not an intermediate in the reaction; (4) the yield of amide decreases in parallel with the increasing length of the side chain; (5) amides are formed either from or concurrently with acids; (6) ammonia, primary and secondary amines may be used as bases; (7) side reactions are (a) complete reduction to aralkyl hydrocarbons, (b) rupture of the side chain to give aryl acids and (c) formation of thiophene derivatives.

More recent information indicates that probably a progressive reaction proceeds along the side chain which will pass a tertiary but not a quaternary carbon atom. King and McMillan (6) showed that the Willgerodt reaction proceeds without rearrangement by converting isobutyrophenone and isovalerophenone to α-methyl-β-phenylpropionamide and α-methyl-γ-phenylbutyramide, respectively. Acetophenone containing C^{13} or C^{14} in the carbonyl group has demonstrated also that no rearrangement occurs in the formation of phenylacetamide (7, 8). The phenylacetic acid, formed in ap-

proximately one-fourth of the amount of the amide, from acetophenone containing C^{14}, however, showed 75% of the initial radioactive carbon in the carboxyl group, thus indicating that it is formed by a different mechanism involving migration of the carbon atom. Pivalophenone, which contains in the side chain a quaternary carbon atom past which no functional group can move, gave no trace of amide but merely neopentylbenzene. King and McMillan (6) interpreted this as indicating that the normal Willgerodt reaction probably proceeds by a progression along the side chain.

Ammonium sulfide is a fairly common reducing agent and sulfur has been used as an oxidizing agent in numerous instances consequently ammonium polysulfide may be both an oxidizing and a reducing agent. King suggested on this basis that the following equilibria may occur.



In support of this mechanism the following compounds were converted to phenylacetamide in the yields indicated: acetophenone (50%), methylphenylcarbinol (48%), styrene (49%), 2-phenylethanethiol (95%). Other ketones, alcohols, olefins and thiols were also used to prove the mechanism (6, 9).

Carmack and DeTar from a detailed study using aqueous ammonia, sulfur and pyridine were able to increase the yield of phenylacetic acid from acetophenone from 63% (Willgerodt) to 86% (10). Using this reagent with phenylacetylene and styrene the respective yields of product were 72% and 64%; 1-phenylpropyne and 1-phenylpropene also reacted smoothly. The yields of amides obtained from ketones and unsaturated hydrocarbons decrease in the follow-

ing order: ketones, acetylenes and olefins (11). When an $(NH_4)_2S_x$ - dioxane reagent was applied to isobutyrophenone the principal product isolated was phenylacetamide. It is significant that cleavage occurred at the point of branching, an indication that the tertiary carbon atom presents a serious obstacle to the normal course of the reaction. They concluded also that the carbon skeleton remains fixed while a labile functional group moves along the chain and eventually undergoes irreversible oxidative conversion into a carboxylic acid derivative when it reaches the end of the chain. No unequivocal evidence is available which establishes the chemical nature of the labile functional group capable of migrating along the chain.

The isolation of any α-methyl-γ-phenylbutyramide from the reaction of isobutyrophenone proves that a mechanism exists by which the branched chain compounds can react without loss of carbon, but the poor yields from this and other branched chain compounds, the occurrence of cleavage reactions at points of branching, and the very markedly higher yields obtained with straight chain starting compounds have been interpreted as pointing to the existence of at least two different mechanisms, one of which can operate effectively only in unbranched alkyl chains. Carmack and DeTar consider it unlikely that acetylenes are first reduced to olefins before being converted into amides. It is also an experimental fact that olefins generate hydrogen sulfide when heated with sulfur or with sulfur and amines to give acetylenes. A reaction mechanism which they have proposed is shown in the following equations (12)

$$R'COCH_2CH_3 + R_2NH \rightleftarrows R'\underset{\underset{NR_2}{|}}{\overset{\overset{OH}{|}}{C}}CH_2CH_3 \rightleftarrows R'\underset{\underset{NR_2}{|}}{C}=CHCH_3 \rightleftarrows R'C\equiv CCH_3 \rightleftarrows$$

$$R'CH=\underset{\underset{NR_2}{|}}{C}CH_3 \rightleftarrows R'CH_2\underset{\underset{NR_2}{|}}{C}=CH_2 \rightleftarrows R'CH_2C\equiv CH \rightleftarrows R'CH_2CH=\underset{\underset{NR_2}{|}}{CH} \xrightarrow{S} R'CH_2CH_2\underset{\underset{NR_2}{|}}{C}=S.$$

Recent Contributions.--1,1-Diphenylethylene, 2-phenylpropene and 1,1-dineopentylethylene give respectively diphenylacetamide, a mixture of α-phenylpropionamide and phenylacetamide, and neopentylacetamide. In the latter two cases the compounds were cleaved and an alkyl group eliminated (13).

Thiosulfates and ammonium sulfite in conjunction with the $(NH_4)_2S_x$ reagent gives improved yields in the Willgerodt reaction (13).

Halogen substituted, alkoxyl substituted and alkylthio substituted aromatic aliphatic ketones function as expected. Hydroxy, acetoxy, amino, acetamino and nitro acetophenones also undergo re-

action in spite of earlier reports that these would not undergo the Willgerodt reaction (14, 15).

The reaction is customarily run in a sealed glass tube. In the Kindler modification using morpholine the reaction could be run under reflux conditions. King and McMillan (14) have made comparative studies of the use of ten amines in the reaction with styrene and sulfur under reflux conditions. Morpholine gives an 84% yield of phenylacetic acid; n-heptylamine and piperidine, approximately 60% yields and 2-ethylhexylamine and cyclohexylamine, 50% yields. The other amines give lower results. Successful experiments were also made with sulfur and aqueous ammonia on a variety of compounds instead of the regular $(NH_4)_2S_x$. This reagent also has been used by Carmack and coworkers.

Bibliography

1. Carmack, Seminar, Feb., 1941.
2. Curtin, Seminar, Dec., 1943.
3. Carmack and Spielman, "Organic Reactions", Vol. III, 1946, p. 83.
4. Cavalieri, Pattison and Carmack, J. Am. Chem. Soc., 67, 1783 (1945).
5. King and McMillan, ibid., 68, 525 (1946).
6. King and McMillan, ibid., 68, 632 (1946).
7. Shantz and Rittenberg, ibid., 68, 2109 (1946).
8. Dauben, Reid, Yankwich and Calvin, ibid, 68, 2117 (1946).
9. King and McMillan, ibid., 68, 1369 (1946).
10. DeTar and Carmack, ibid., 68, 2025 (1946).
11. Carmack and DeTar, ibid., 68, 2029 (1946).
12. Reference (3) p. 88.
13. Pattison and Carmack, J. Am. Chem. Soc., 68 2033 (1946).
14. King and McMillan, ibid., 68, in press (1946).
15. Ott, Mantano and Coleman, ibid., 68, in press (1946).

Reported by Gerhard W. Leubner
November 8, 1946

THE CONSTITUENTS OF POISON IVY

Historical Facts

Poison ivy, which is perhaps the most widely known of all the American poisonous plants, is found in nearly all parts of the United States and Canada.

Perhaps the earliest recorded attempt to isolate the ingredients of poison ivy responsible for its dermatitis properties was made by Khittel (1) in 1858. He could not identify the product, but thought the poison was a volatile alkaloid. In 1866 Maisch (2) obtained a volatile acid from the plant by steam distillation, but secured no definite physiological evidence that this was the poison. In fact some 31 years later Pfaff (3) pointed out that this acid obtained by Maisch was nothing more than impure acetic acid containing traces of the poison.

Acree and Syme (4) in 1906 came to a conclusion that it was a glycoside, but this was refuted by McNair (5) in 1916 who worked with poison oak and in 1921 (6) showed that the ingredient of this plant responsible for its dermatitis properties was some type of an o-dihydroxybenzene derivative, but he could not identify it. Analysis showed that it contained only carbon, hydrogen, and oxygen. He showed the presence of the hydroxy groups by preparing acetyl derivatives either by the treatment of the ingredient with acetyl chloride in a benzene medium or by treatment with sodium acetate and acetic anhydride. He also obtained a benzoyl derivative with benzoyl chloride by the Schotten-Baumann method. The dermatitant indicated the presence of an ortho-dihydric phenol since an alcoholic solution of it assumed a color varying from green to brown when treated with sodium or potassium hydroxide, and a highly dilute alcoholic solution gave a green color with ferric chloride which turned red on the addition of sodium carbonate.

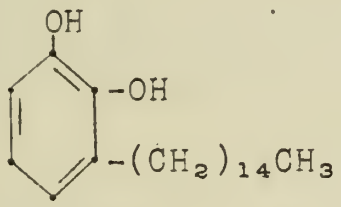
Hill and his coworkers (7) in 1934 finally isolated it in sufficiently pure form to enable them to identify the vesicant oil as urushiol, a material isolated by Riko Majima (8) from the sap of the Japanese lac tree. Majima showed the structure of urushiol to be a mixture of pyrocatechol derivatives as is indicated in subsequent paragraphs. Keil, Wasserman, and Dawson (9) in 1944 indicated that biological evidence supports the view that the active ingredient is a pyrocatechol derivative with a long side chain in the 3 position. Stevens (10) points out that the saps of ivy, sumac, oak, and lac trees all probably contain an oily material urushiol, of which 0.001 mg. can cause dermatitis in sensitive people.

Structure of Urushiol

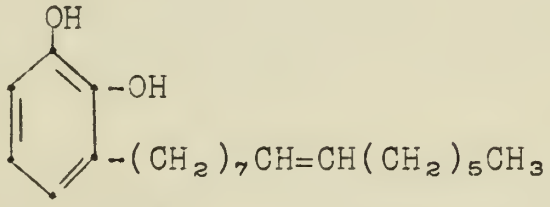
In Japan many manufactured wooden articles are lacquered with the sap obtained from the lac tree. Since this sap possesses a vesicant nature which often incapacitates the workers by very bad rashes and blistered skins, Majima became interested in its structure and conducted an extensive investigation during the years 1906

to 1922. He extracted the sap by means of alcohol and petroleum ether. After removal of the solvents, he distilled the residue in a vacuum and obtained an oil, which he termed urushiol, giving the typical reactions associated with a 1,2-dihydroxybenzene derivatives, i.e., reduction of ammonical silver nitrate solution, a white precipitate of the lead salt with lead acetate, and a dark green to black color with ferric chloride.

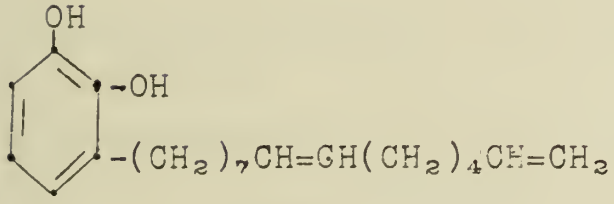
Majima concluded for reasons indicated below that urushiol is probably a mixture of catechols which he could not separate by distillation - a small quantity of saturated material (A) being present, dissolved in at least two unsaturated substances (B) and (C) with double bonds in an aliphatic chain, and possibly accompanied by a more highly unsaturated substance (D).



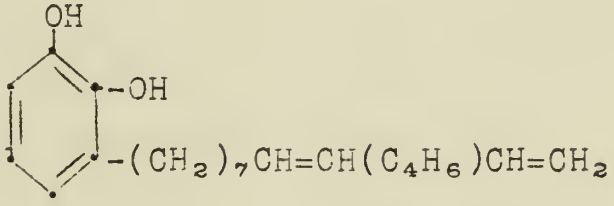
(A)



(B)



(C)



(D)

1. When urushiol was reduced, all of the components were converted into a single substance, 1-n-pentadecyl-2,3,dihydroxybenzene, called hydrourushiol, the structure of which was established by the synthesis of its dimethyl ether by condensation of 2,3-dimethoxyphenylpropionyl chloride with the sodium derivative of 1-dodecyne followed by reduction of the acetylenic ketone (16).

2. By heating hydrourushiol over a free flame or at 350-400°C in a sealed tube, only catechol could be isolated from the decomposition products (17).

3. Oxidation of hydrourushiol with permanganate in cold aqueous acetone yielded palmitic acid, indicating the side chain must be $C_{15}H_{31}$ (17,18).

4. Oxidation of urushiol by various methods yielded formic acid, acetaldehyde, heptaldehyde, and the acid $C_6H_3(OH)_2(CH_2)_7CO_2H$.

5. Absorption of bromine in carbon tetrachloride by urushiol dimethyl ether yielded a product that was not homogeneous.

6. Quantitative hydrogenation of urushiol showed an average of two aliphatic double bonds.

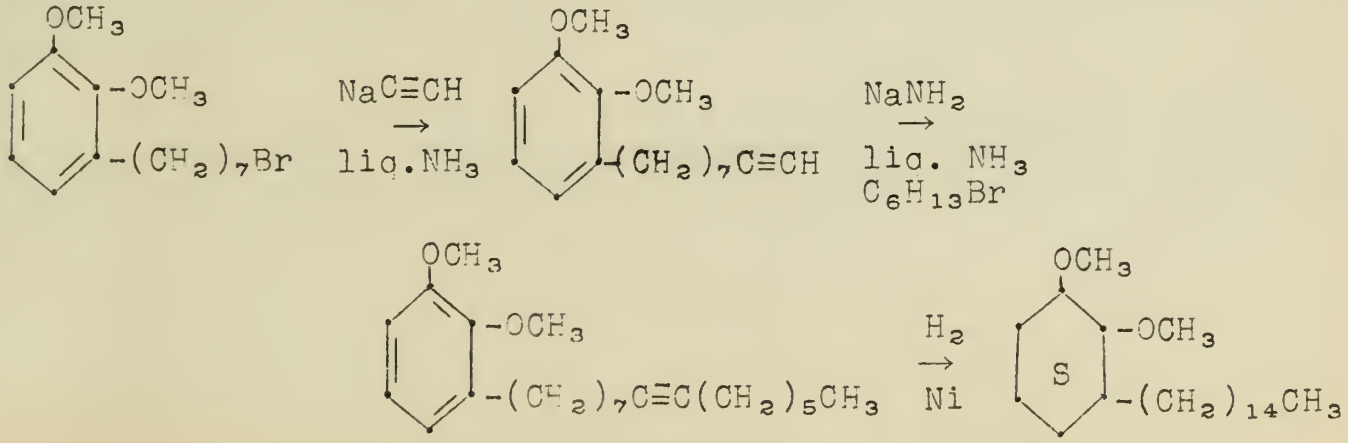
Constituents of Poison Ivy.

Hill and his coworkers (7) in 1934 undertook the isolation and identification of the toxic ingredient of poison ivy. They isolated material, indicative of the presence of a 1,2-dihydroxybenzene structure which had a boiling point, analysis, and molecular weight that agreed with urushiol.

To establish the identity of the poison ivy extract with urushiol, a group of derivatives was prepared. The dimethyl ether of the ivy oil closely resembled urushiol dimethyl ether. The unsaturated oil from poison ivy was reduced catalytically and yielded a solid material identical with hydrourushiol. The dimethyl ether, the diacetate and the dibenzoate of this solid yielded in each instance products which seemed to be identical with those of the corresponding substance prepared from hydrourushiol. A tabulation of certain derivatives of urushiol with those of similarly constituted products of poison ivy is given below.

		"poison ivy urushiol series"
1. Urushiol	B.P. 210°C (0.5 mm)	B.P. 210°C (0.4-0.6 mm)
2. Urushiol dimethyl ether	B.P. 208°C (1.2 mm)	B.P. 190-195°C (0.3-0.6 mm)
3. Hydrourushiol	M.P. 58.9-59°C	M.P. 59°C
4. Hydrourushiol dimethyl ether	M.P. 36-37°C	M.P. 36.2-37°C.
5. Hydrourushiol diacetate	M.P. 50-51°C	M.P. 50.2°C
6. Hydrourushiol dibenzoate	M.P. 59.5-60.5°C	M.P. 59-60.5°C

Wasserman and Dawson (15) in 1942 prepared tetrahydrourushiol dimethyl ether by preparing 3(7'-bromoheptyl)veratrole and then proceeding by the set of reactions as indicated below. This



synthetic product was found to be identical with the compound obtained by Hill through the methylation and catalytic reduction of urushiol isolated from poison ivy.

Compounds B, C, and D have not been synthesized to date. Wasserman and Dawson attempted to prepare B, but obtained only an impure compound that could not be purified by distillation. Mason and Schwartz (11) have indicated they are engaged in improving techniques with the view of preparing these compounds and of separating compounds B, C, and D from the isolated toxic ingredient of poison ivy.

Physiological Effects of the Constituents of Poison Ivy.

Hill made tests on the physiological activity of some of the ivy products. The unsaturated dihydroxy compound is exceedingly toxic, causing the characteristic dermatitis poisoning, whereas the dimethyl ether from this oil is non-toxic. The saturated dihydroxy compound is only slightly less toxic than the unsaturated analog, while the dimethyl ether of the saturated phenol is without toxic action. Thus this indicates that the hydroxy groups in urushiol are the chief cause of its well known violent vesicant action.

More recently, Keil and his coworkers (9) in 1944 have shown group reactions in patients sensitive to poison ivy leaves or extracts were exhibited by the following compounds.

Compounds	%	Number of Cases
3-pentadecylpyrocatechol	100	21
urushiol dimethyl ether	33	33
3-pentadecenyl-1'-veratrole	21	21
3-methylpyrocatechol	14	21
hydrourushiol dimethyl ether	10	20

3-Geranylpyrocatechol shows a practically constant group reactivity. No group sensitivity was demonstrated with 4,5-dimethylpyrocatechol, and insignificant responses were shown by pyrocatechol, 4-methylpyrocatechol, and 4-tertiarybutyl pyrocatechol. 4-Pentadecylveratrole was inactive.

It is interesting to note that 3-pentadecylpyrocatechol was active although it contains a saturated side chain and that the 4-isomer gave some positive reactions, though they were less intense and less frequent.

Bibliography

1. Am. J. Pharm., 6 (3), 542 (1858).
2. ibid., 14 (3), 4 (1866).
3. J. Exp. Med., 2, 181 (1897).
4. J. Biol. Chem., 2, 547 (1906).
5. J. Am. Chem. Soc., 38, 1417 (1916).
6. ibid., 43, 159 (1921).
7. ibid., 56, 2736 (1934).
8. Ber., 42, 1418 (1908).
9. J. Exptl. Med., 80, 275 (1944).
10. J. Am. Med. Assoc., 127, 912 (1945).
11. J. Am. Chem. Soc., 64, 3058 (1942).
12. ibid., 66, 1156 (1944).
13. ibid., 67, 1233 (1945).
14. J. Chem. Education, 20, 448 (1943).
15. J. Org. Chem., 8, 73 (1943).
16. Ber., 48, 1606 (1915).
17. Ber., 46, 4080 (1913).
18. Ber., 48, 1593 (1915).
19. Ber., 55 (B), 172 (1922).

Reported by Carl Weatherbee
November 15, 1946

THE CHUGAEV REACTION

The Chugaev reaction consists in the formation of an olefin from an alcohol through the intermediate formation of a xanthate. This procedure is especially useful for the conversion to olefins of those alcohols which undergo rearrangement by the usual dehydration methods.

Xanthates (ROCSSR) have been prepared by the following methods:

					Reference
RI	$\xrightarrow{KOH,\ CS_2}$	ROCSSR			4
ROK	$\xrightarrow{CS_2}$	ROCSSK	$\xrightarrow{R'I}$	ROCSSR'	11, 16
ROH	$\xrightarrow{NaOH,\ CS_2}$	ROCSSNa	$\xrightarrow{R'I}$	ROCSSR'	21

Closely related to the xanthates are the isomeric dithiocarbonates (RSCOSR), which, although they are more stable than the xanthates, give the same thermal decomposition products (2,9). The dithiocarbonates sometimes result from the primary decompositions of the xanthates and have been prepared by the following methods:

					Reference
$2RCNS + 3H_2O \rightarrow$	RSCOSR	$+ CO_2 + 2NH_3$			17
$2RSNa + COCl_2 \rightarrow$	RSCOSR	$+ 2NaCl$			15
$RSNa + COCl_2 \rightarrow$	$NaCl + RSCOCl$		$\xrightarrow{R'SNa}$	RSCOSR'	2

These isomeric compounds are best distinguished by treatment with phenylhydrazine which has no action on a dithiocarbonate while it reacts with a xanthate as follows: (20)

$$ROCSSR' + C_6H_5NHNH_2 \rightarrow ROCSNHNHC_6H_5 + R'SH$$

In the Chugaev reaction the xanthates undergo thermal decomposition, yielding an unsaturated hydrocarbon, carbonyl sulfide, and a mercaptan. This decomposition is usually accomplished by the destructive distillation of the xanthate. A few examples are listed in Table I.

TABLE I

R in $ROCSSCH_3$	Unsat. Hydrocarbon	Reference
menthyl	menthene	6, 3
cyclohexylmethyl	methylenecyclohexane	1
iso-amyl	iso-propylethylene	21
pinacolyl	t-butylethylene	15

The usual type of decomposition cannot occur when there is no hydrogen atom on the second carbon atom from the oxygen of the xanthate group. Laasko[9] prepared O-2,2,6,6-tetramethylcyclohexyl-S-methyl xanthate and found that when heated to 230° it

merely rearranged to form the isomeric dithiocarbonate. Nametkin and Kursanov[13] obtained stilbene from the thermal decomposition of O-benzyl-S-methyl xanthate. Kursanov[8] obtained tetraphenylethylene from O-benzhydryl-S-methyl xanthate, while Stevens and Richmond[19] obtained diphenylmethane and tetraphenylethane from the same compound. Bulmer and Mann[2] studied the thermal decomposition of various benzyl and p-substituted benzyl xanthates and dithiocarbonates. Their results are shown by the following equation:

$$\text{p-ClC}_6\text{H}_5\text{CH}_2\text{OCSSCH}_2\text{C}_6\text{H}_5 \xrightarrow{\triangle} \text{C}_6\text{H}_5\text{CH}_2\text{SSCH}_2\text{C}_6\text{H}_5 + \text{ClC}_6\text{H}_5\text{CH CHC}_6\text{H}_5\text{Cl}$$

$$\text{p-ClC}_6\text{H}_5\text{CH}_2\text{OCSSCH}_2\text{C}_6\text{H}_5\text{CH}_3 \xrightarrow{\triangle} \text{ClC}_6\text{H}_5\text{CH CHC}_6\text{H}_5\text{Cl} + \text{CH}_3\text{C}_6\text{H}_5\text{CH CHC}_6\text{H}_5\text{CH}_3$$

$$\text{C}_6\text{H}_5\text{CH}_2\text{SCOSCH}_2\text{C}_6\text{H}_5 \xrightarrow{\triangle} \text{C}_6\text{H}_5\text{CH}_2\text{SSCH}_2\text{C}_6\text{H}_5$$

Isomeric compounds gave the same decomposition products in all cases. Attempts to prepare dibenzyl xanthate resulted in the formation of dibenzyl disulfide, indicating that this xanthate is not stable. In some cases the xanthates and dithiocarbonates distilled at 0.1-0.5 mm. yielding a form of the dithiocarbonate that differed only in thermal stability.

Bibliography

1. Alexandrovitsch, J. Gen. Chem. (U. S. S. R.), 3, 38 (1923).
2. Bulmer and Mann, J. Chem. Soc., 1945, 666.
3. Chugaev, Ber., 31, 1775 (1898); 32, 3332 (1899); 33, 735, 3118 (1900); 34, 2276 (1901); 37, 1481 (1904); 42, 4631 (1909); 45, 1293 (1912). Ann., 375, 288 (1910); 388, 280 (1912). J. Russ. Phys, Chem. Soc., 35, 1116 (1903); 36, 988 (1904).
4. Debus, Ann., 75, 127 (1850).
5. Fomin and Sochenski, Ber., 46, 246 (1913).
6. Huckel, Tapp, and Leguthe, Ann., 543, 191 (1940).
7. Kosternaya, Uchenye. Zapiski Leningrad Gosudorst. Univ. Ser. Khim. Nauk., 3, 126 (1938); C. A., 33, 3760 (1939).
8. Kursanov, J. Russ. Phys. Chem. Soc., 60, 921 (1928).
9. Laasko, Suomen Kemistilehti, 13B, 8 (1940); C.A., 34, 5059 (1940
10. McAlpine, J. Chem. Soc., 1931, 1114; 1932, 906.
11. Mylius, Ber., 5, 972 (1872).
12. Nametkin and Brussov, Ber., 56, 1807 (1923).
13. Nametkin and Kursanov, J. pr. Chem., 112, 164 (1926). J. Russ. Phys. Chem. Soc., 57, 390 (1926).
14. Qvist, Ann., 417, 278 (1918).
15. Salomon, J. pr. Chem., 6, 444 (1872); 8, 114 (1873).
16. Scala, Gazz. Chim. Ital., 17, 81 (1887).
17. Schmidt and Glutz, Ber., 1, 166 (1872).
18. Schone, J. pr. Chem., 92, 244 (1885).
19. Stevens and Richmond, J. Am. Chem. Soc., 63, 3132 (1942).
20. Wheeler and Barnes, Am. J. Chem., 24, 60 (1900).
21. Whitmore and Simpson, J. Am. Chem. Soc., 55, 3809 (1933).

Reported by George Munn
November 15, 1946.

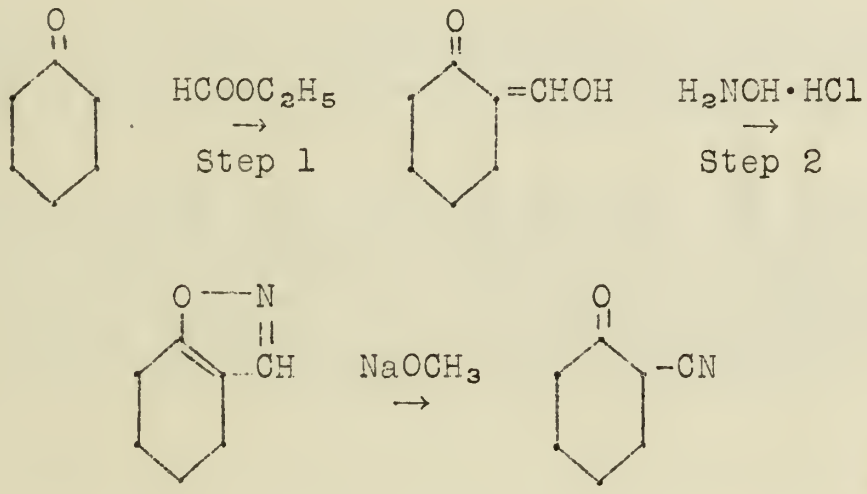
A PLAN FOR DISTINGUISHING BETWEEN SOME FIVE- AND SIX-MEMBERED RING KETONES

During the course of a study of the reaction of α-hydroxymethylene ketones with hydroxyl amine, a striking difference in the behavior of cyclohexanone and cyclopentanone derivatives was observed by Johnson and coworkers (1). This difference has been taken advantage of, and the following scheme to distinguish the two types of compounds was devised.

1. Condensation of the ketone with ethyl formate,
2. Treatment of the hydroxymethylene ketone with hydroxylamine hydrochloride in acetic acid,
3. Examination of the condensation products.

In the cases studied it has been found that the cyclohexanone derivatives reacted according to the conventional scheme "A" giving rise to oxazoles at step (2). These substances were non-acidic and readily converted to acidic β-ketonitriles. The formation of

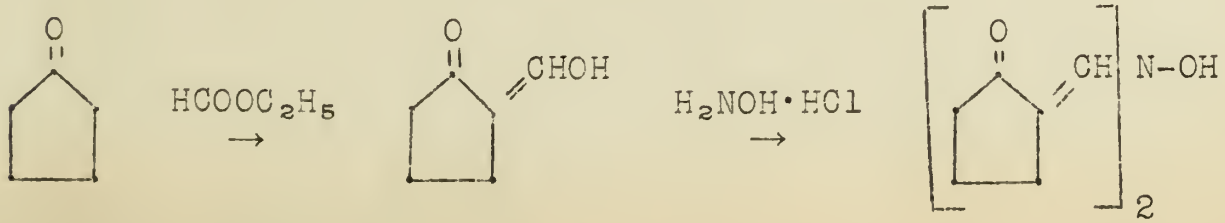
Scheme A



isoxazoles from open chain α-hydroxymethylene ketones and hydroxylamine is well known (2, 3). That the generality of this reaction extends to cyclohexanone derivatives is indicated by previous work (4).

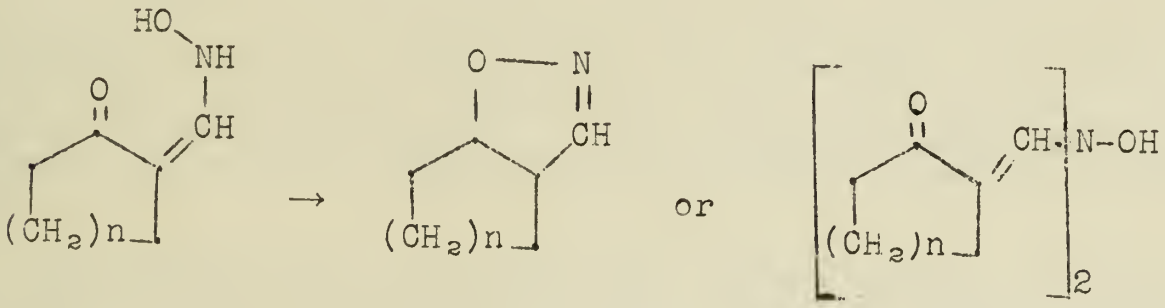
In sharp contrast the cyclopentanone derivatives (see scheme B) condensed to form di-substituted hydroxylamine derivatives.

Scheme B



The reaction of a hydroxymethylene ketone with hydroxylamine most probably involves the initial formation of an oxime. The fate of this intermediate would seem to depend upon at least two competing reactions.

1. Intramolecular dehydration to give isoxazole (I) or
2. Condensation with reactive hydroxymethylene ketone to form (II).



Oxime I II

The former appears to take precedence when the cyclization is unhindered as in the case of six-membered ring ketones. With five-membered ring, however, the intermolecular reaction seems to predominate.

It should be pointed out, in conclusion, that the cyclopentanone derivatives which have been studied gave rise to condensation products which were insoluble in the reaction medium and were, therefore, easily isolated. It is recommended that when used as a diagnostic test, the reaction between hydroxymethylene ketone and hydroxylamine be conducted at room temperature.

Bibliography

1. W. S. Johnson and E. Shelberg, J. Am. Chem. Soc., 67, 1745 (1945).
2. Claisen, Ber., 36, 3664 (1903).
3. Claisen, Ber., 42, 59 (1909).
4. v. Auwers, Bahr and Frese, Ann., 441, 54 (1925).

Reported by N. Shanmukha Rao
November 22, 1946

SYNTHESIS OF BRANCHED-CHAIN FATTY ACIDS

Although branched-chain fatty acids rarely occur in nature, there has been special interest in those that do occur. Determination of the structure of branched-chain fatty acids has been rendered difficult by the lack of knowledge of the properties of pure synthetic branched-chain acids.

The natural occurring acids are of both chemical and physiological interest, yet very little is known concerning their structure except tuberculostearic acid which is probably 10-methyl octadecanoic acid. Although isostearic, isopalmitic, isomyristic, and several 10-methyl and 2-methyl acids had been synthesized, in no case had the physical properties of an entire series of branched-chain acids been investigated. James Cason and his coworkers inaugurated the task of synthesizing the series of methylstearic acids.

Cason found that the method best adapted to the synthesis of this series was the reaction between a dialkyl cadmium compound and ω carbethoxynonoyl chloride. The resulting keto ester was then reduced by the Clemmensen reduction to the acid. The synthesis of the methylstearic acids thus reduces to the preparation of the desired dialkyl cadmium compound.

For the synthesis of 17-methyloctadecanoic acid the necessary bromide is isononyl prepared as indicated by the following equations:

$$(CH_3\underset{CH_3}{\underset{|}{C}}HCH_2CH_2)_2Cd + 2ClCOCH_2CH_2CO_2CH_3 \xrightarrow[78\%]{\text{Benzene}} 2CH_3\underset{CH_3}{\underset{|}{C}}H(CH_2)_2CO(CH_2)_2CO_2CH_3$$

$$\xrightarrow[79\%]{Zn(Hg),\ HCl} 2CH_3\underset{CH_3}{\underset{|}{C}}H(CH_2)_5CO_2H \xrightarrow[89\%]{C_2H_5OH,\ H_2SO_4} 2CH_3-\underset{CH_3}{\underset{|}{C}}H(CH_2)_5CO_2C_2H_5$$

$$\xrightarrow[57\%]{Na,\ C_2H_5OH} 2CH_3\underset{CH_3}{\underset{|}{C}}H(CH_2)_6OH \xrightarrow[91\%]{HBr,\ H_2SO_4} 2CH_2\underset{CH_3}{\underset{|}{C}}H(CH_2)_6Br$$

The isononyl bromide was used for the preparation of Grignard reagent which in turn was treated with cadmium chloride to obtain the desired diisononyl cadmium.

$$[CH_3\underset{CH_3}{\underset{|}{C}}H(CH_2)_6]_2Cd + 2ClCO(CH_2)_8CO_2C_2H_5 \xrightarrow[46\%]{\text{Ether}} 2CH_3\underset{CH_3}{\underset{|}{C}}H(CH_2)_6CO(CH_2)_8CO_2C_2H_5$$

$$\xrightarrow[77\%]{Zn(Hg)HCl} 2CH_3\underset{CH_3}{\underset{|}{C}}H(CH_2)_{15}CO_2H$$

By distillation of a portion of the ether from the diisononyl cadmium and running the reaction in benzene the yield of ethyl 10-keto-17-methyloctadeanoate may be increased greatly. In most cases where benzene is substituted for ether the yields are as high as 70-84% as based on the acid chloride. This increased yield in benzene solution is due to, less loss of the dialkyl cadmium reagent through enolization of the ketone, reduction of the diester formation, and better mechanical stirring.

In the synthesis of 16-methyloctadecanoic acid, the required 1-bromo-6-methyl octane was prepared from 2-methyl butanol-1 by the same method used for isononyl bromide. The 16-methyloctadecanoic acid prepared by this method was contaminated with the 17-methyl isomer which could not be removed. 1-Bromo-6-methyloctane was prepared by a method involving no branched-chain starting materials. Overall yield from 6-ketoheptoate was 19-30%.

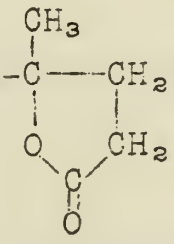
$$C_2H_5MgI + CH_3\overset{O}{\overset{\|}{C}}(CH_2)_4CO_2C_2H_5 \rightarrow C_2H_5\overset{OH}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}(CH_2)_4CO_2C_2H_5 \xrightarrow[\Delta]{I_2}$$

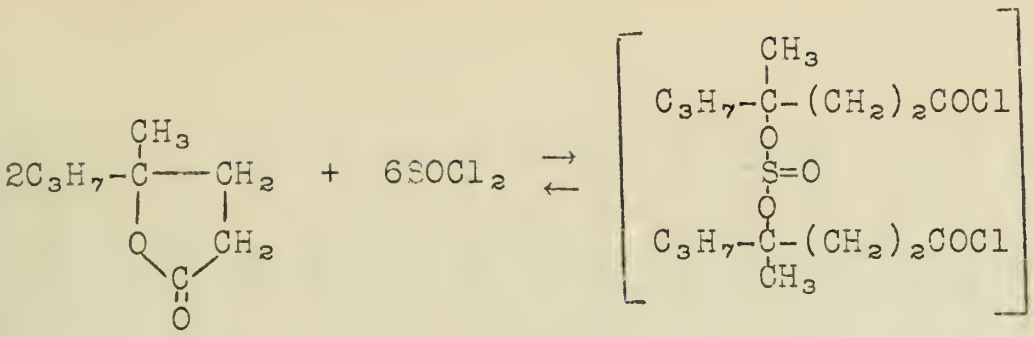
$$C_2H_5C(CH_3) = CH(CH_2)_3CO_2C_2H_5 \xrightarrow[Ni]{H_2} C_2H_5CH(CH_3)(CH_2)_4CO_2C_2H_5$$

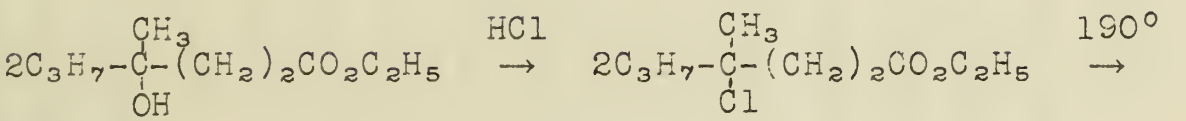
16-Methyloctadecanoic acid synthesized using 1-bromo-6-methyloctane prepared by the latter method was readily purified.

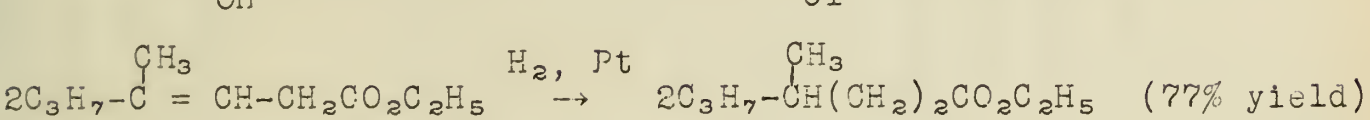
For the synthesis of 15-methyloctadecanoic acid, 1-bromo-5-methyloctane was prepared from 2-bromopentane by extension of the chain twice by means of the conventional reaction of a Grignard reagent and ethylene oxide. 1-Bromo-5-methyloctane was also prepared by a procedure involving no branched-chain starting material or secondary halide.

$$2CH_3CO(CH_2)_2CO_2C_2H_5 + 2C_3H_7MgBr \xrightarrow[73\%]{\text{Benzene and ether}} 2C_3H_7\text{-}\underset{\displaystyle O}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}\!\!-\!\!-\!\!\underset{\displaystyle CH_2}{\overset{\displaystyle CH_2}{\overset{|}{\underset{|}{\quad}}}}$$



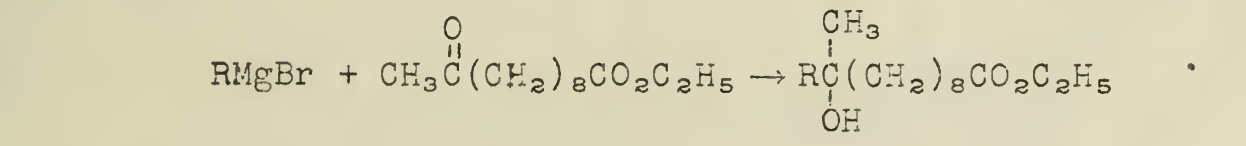




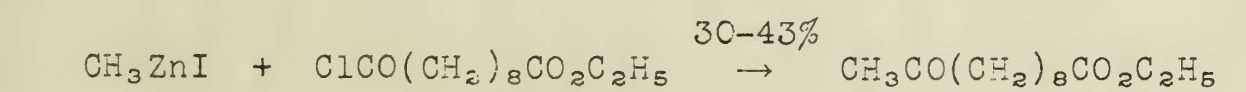


By use of the resulting 5-methyl-heptyl magnesium bromide and formaldehyde, 5-methyloctanol-1 was obtained. 15-Methyloctadecanoic acid, synthesized from 1-bromo-5-methyloctane which was prepared by either of the above methods, had a melting point of 41-43.5. Cason attributated the broad melting point to polymorphic forms rather than the presence of impurities. 14-Methyltetracosanoic acid was prepared by the same general method by starting with γ-decyl-γ-methylbutyrolactone.

10-Methyldocosanoic, 10-methyltetracosanoic, and 10-methyl hexacosanoic acid have been prepared by Schneider and Spielman as indicated. 6-Methyltetracosanoic acid was also prepared by



this general method. The ethyl 10-ketoundeanoate was prepared as follows:



It has since been shown by Cason that by use of the dimethyl cadmium compound, removal of as much ether as possible, and by running the reaction in benzene that the yields of keto esters are generally increased to 75-85%.

2-Methylstearic, 2-methyleicosanoic, 2-methyldocosanoic, 2-methyltetracosanoic, and 2-methylhexacosanoic acid were prepared by Schneider and Spielman by the following procedure.

LIST OF ACIDS CONSIDERED IN SEMINAR

Name of Acid	Structure	Melting Point °C
17-methyloctadecanoic	$CH_3CH(CH_2)_{15}CO_2H$	67.0-67.6
16-methyloctadecanoic	$C_2H_5CH(CH_2)_{14}CO_2H$	49.9-50.6
15-methyloctadecanoic	$CH_3(CH_2)_2-CH(CH_2)_{13}CO_2H$	41.0-43.5
14-methyltetracosanoic	$CH_3(CH_2)_9CH(CH_2)_{12}CO_2H$	57.9-58.5
10-methyldocosanoic	$CH_3(CH_2)_{11}CH(CH_2)_8CO_2H$	45.5-46.0
10-methyltetracosanoic	$CH_3(CH_2)_{13}CH(CH_2)_8CO_2H$	51.0
10-methylhexacosanoic	$CH_3(CH_2)_{15}CH(CH_2)_8CO_2H$	54.0-55.0
2-methyleicosanoic	$CH_3(CH_2)_{17}CHCO_2H$	61.5-62.0
2-methyldocosanoic	$CH_3(CH_2)_{19}CHCO_2H$	67.0-67.5
2-methyltetracosanoic	$CH_3(CH_2)_{21}CHCO_2H$	72.0-72.5
2-methylhexacosanoic	$CH_3(CH_2)_{23}CH-CO_2H$	75.5-76.0
2-methylstearic	$CH_3(CH_2)_{15}CHCO_2H$	54.5
10-methylstearic	$CH_3(CH_2)_7CH(CH_2)_8CO_2H$	20.0-21.0
6-methyltetracosanoic	$CH_3(CH_2)_{17}CH(CH_2)_4CO_2H$	55.8-56.6
16-methylheptadecanoic (isostearic)	$CH_3CH(CH_2)_{14}CO_2H$	67.6-68.2
14-methylpentadecanoic (isopalmitic)	$CH_3CH-(CH_2)_{12}CO_2H$	61.8-62.4
12-methyltridecanoic (isomyristic)	$CH_3CH(CH_2)_{10}CO_2H$	50.5-51.5

$$CH_3CH(CO_2C_2H_5)_2 + RI \rightarrow RC(CH_3)(CO_2C_2H_5)_2 \xrightarrow[\text{decarboxylation}]{\text{Hydrolysis}} RCH(CH_3)CO_2H$$

Synthetic dl-10-methylstearic acid prepared by Spielman closely resembled tuberculostearic acid.

10-Ketostearic acid, obtained by use of octyl zinc chloride on ω carbethoxynonoyl chloride, was converted to the barium salt and reacted with methyl magnesium bromide to give 10-methyl-10-hydroxystearic. Dehydration followed by hydrogenation gave dl-10-methylstearic acid.

Fordyce and Johnson synthesized isopalmitic and isostearic acid by use of isohexyl magnesium bromide and isooctyl magnesium bromide on sebacyl chloride. The resulting keto acid was reduced by Clemmensen reduction. Isomyristic acid was obtained in better yields by use of 9-carbethoxynonoyl chloride.

Bibliography

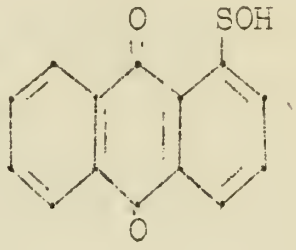
1. Cason, J. Am. Chem. Soc., 64, 1106 (1942).
2. Cason and Prout, ibid., 66, 46 (1944).
3. Cason, Adams, Bennett and Registrer, ibid., 66, 1764 (1944).
4. Cason, ibid., 68, 2078 (1946).
5. Schneider and Spielman, J. Biol. Chem., 142, 345 (1942).
6. Spielman, ibid., 106, 87 (1934).
7. Fordyce and Johnson, J. Am. Chem. Soc., 55, 3368 (1933).

Reported by Rupert E. Light, Jr.
November 22, 1946

SULFENIC ACIDS AND THEIR DERIVATIVES

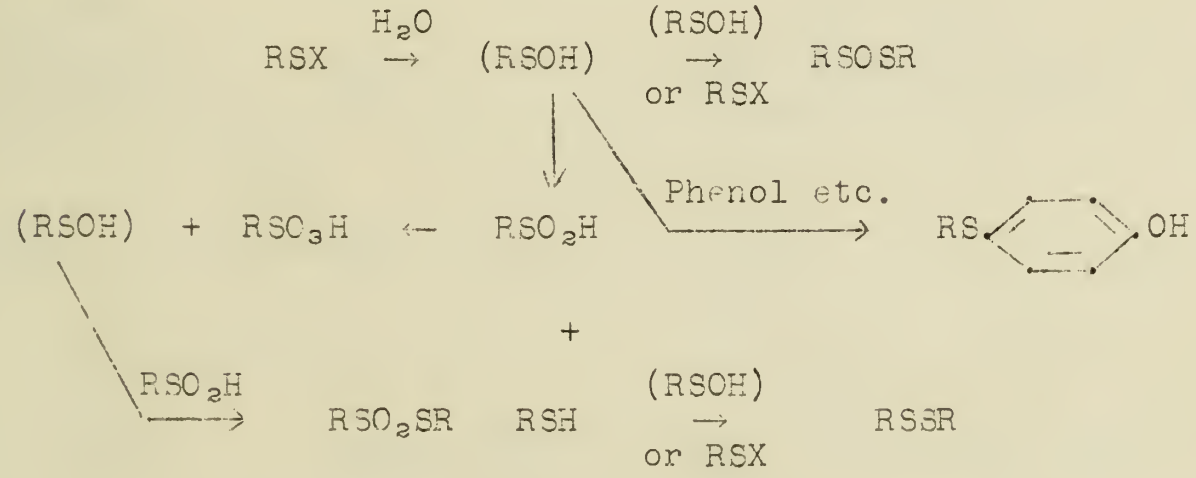
Sulfenic acids are very reactive and unstable, giving rise to a variety of products including sulfinic acids, disulfides, sulfenic anhydrides and thiolsulfonic esters (1). The generally accepted formula of sulfenic acids is RSOH representing an organic acid of bivalent sulfur. However, it is possible that this structure may be convertible to a "pseudo" form, $RSO\overset{H}{}$ as indicated by reactions of the alkali salts (2). The only successful isolation of a sulfenic acid was reported by Fries (3) in 1912. He was able to synthesize 1-anthraquinonesulfenic acid by a series of reactions starting with the corresponding halide as shown by the following steps.

$$RCl \xrightarrow{Na_2S_2} RSSR \xrightarrow{Br_2} RSBr \xrightarrow{CH_3OH} RSOCH_3 \xrightarrow{KOH} RSOK \xrightarrow{H^+}$$



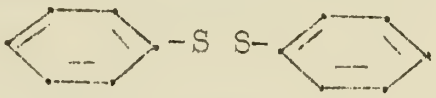
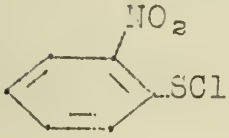
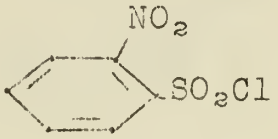
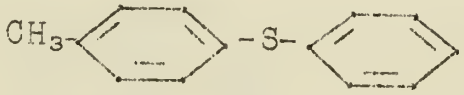
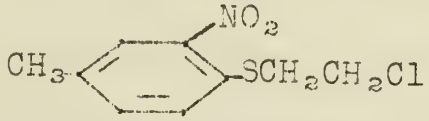
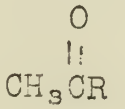
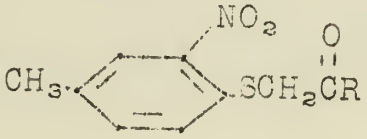
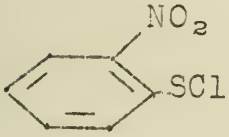
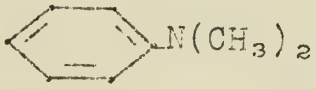
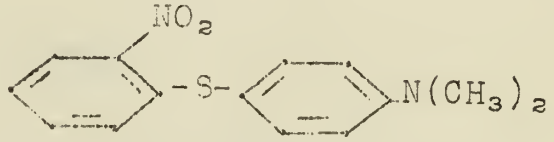
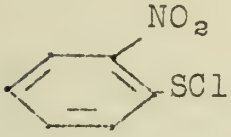
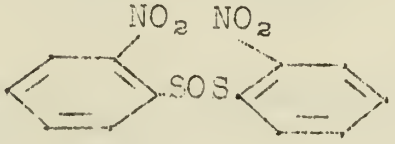
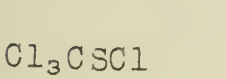
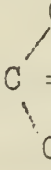
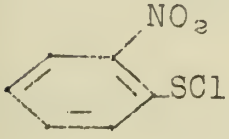
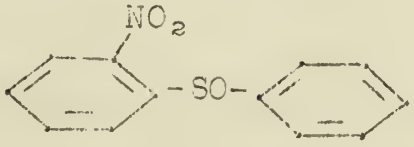
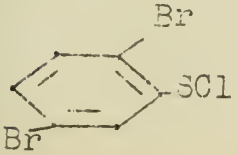
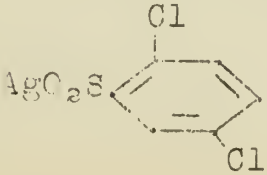
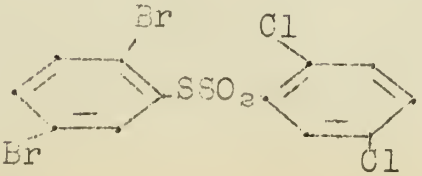
It may be supposed that a strong tendency for hydrogen bonding (1) is a factor in the stability of this compound.

Even though only one sulfenic acid has been isolated, the ability to predict correctly the products of various reactions by this intermediate leads to the supposition that compounds of this structure may be involved as shown below.

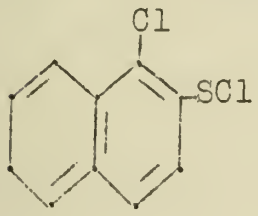
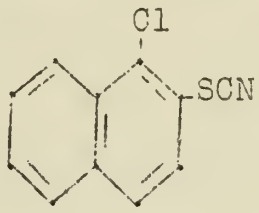
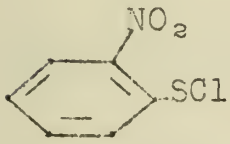
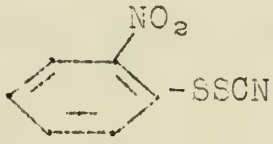


Sulfenyl halides which may be regarded as the acid halide derivatives of sulfenic acids are most commonly prepared by the action of halogens (chlorine and bromine) on the corresponding disulfides, sulfides and mercaptans (1, 3, 4, 5, 6) in inert solvents. Sulfenyl bromides are also prepared by treating sulfinic acid (3) with hydrogen bromide. Some of the reactions of sulfenyl halides are summarized in the following table.

REACTIONS OF SULFENYL HALIDES

Sulfenyl Halide	Reagent	Product	Reference
	Zn		7
	Cl_2 in HOAC		8
			9
	$CH_2 = CH_2$		9
			5
			10
	H_2O		10
	H_2O		11
			10
			12

REACTIONS OF SULFENYL HALIDES (CONTINUED)

Sulfenyl Halide	Reagent	Product	Reference
	KCN		5, 10
	KSCN or $(SCN)_2$		6

Sulfenamides, another important class of sulfenic acid derivatives, may be briefly described by the following equations in which R may be an alkyl or aryl group as well as hydrogen. However, if the amine reagent is too weakly basic there is no reaction (2, 7, 8, 9, 10, 13, 14).

$$ArSX + HNR_2 \rightarrow ArSNR_2$$

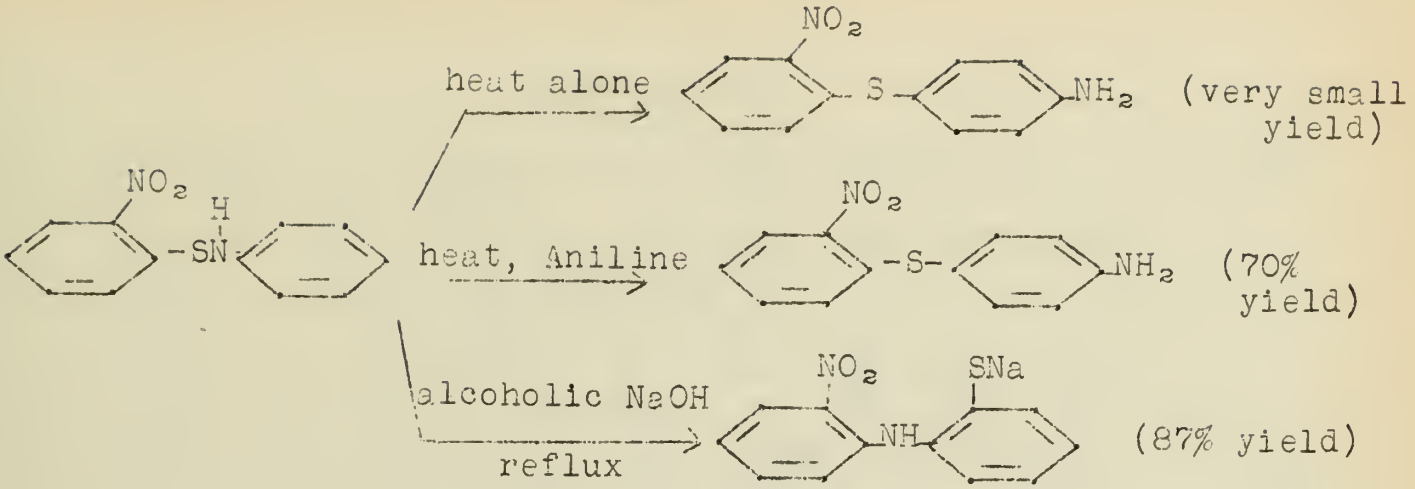
$$ArSH + HNR_2 \xrightarrow{(O)} ArSNR_2 + ArSSAr$$

The sulfenamides, unlike the sulfonamides, are weakly basic, but not sufficiently basic to form hydrochloride salts (14). Some of their typical reactions are summarized below.

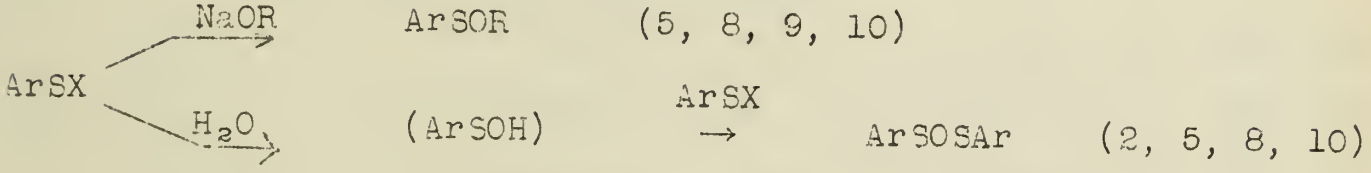
$$ArSNR_2 \xrightarrow{HCl\ (anhyd.)} ArSCl + R_2NH\cdot HCl \quad \text{(almost theoretical)} \quad (13, 14)$$

$$ArSNR_2 \xrightarrow[aqueous\ HCl]{alcoholic\ or} ArSSAr + R_2NH\cdot HCl \quad (15, 16)$$

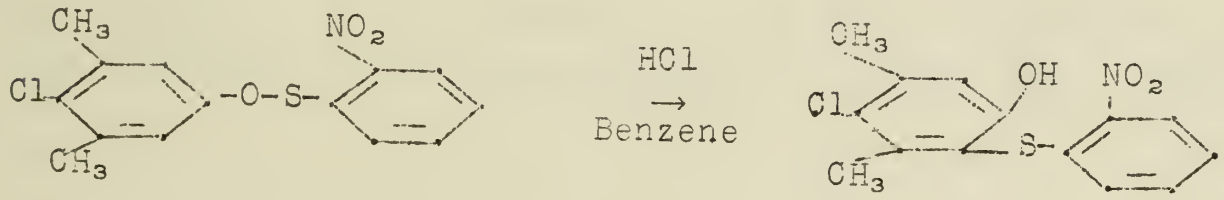
Sulfenamides may also undergo rearrangement by heating with suitable reagents (15, 16, 17, 18, 19).



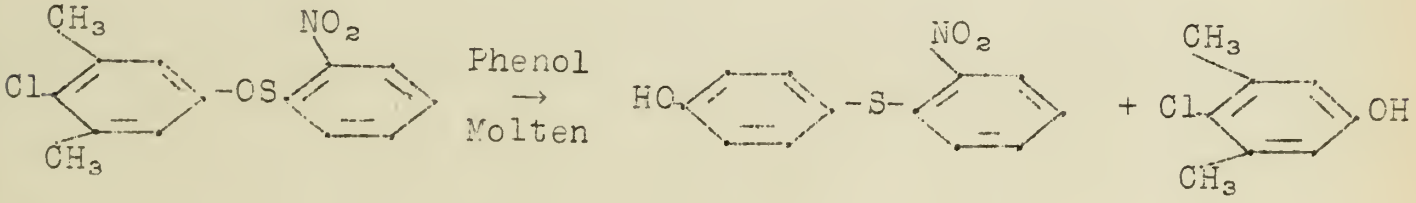
The sulfenic esters and anhydrides may be formed from sulfenyl halides.



Sulfenic esters may undergo rearrangement in the presence of hydrogen chloride in benzene solution (20).



It was also found (20) that an external phenol could displace the original aryl group of the sulfenate showing that the rearrangement is not a true intramolecular rearrangement.



An excellent review of sulfenic acids and their derivatives was recently published by Kharasch, Potempa and Wehrmeister (1).

Bibliography

1. Kharasch, N., Potempa, S. J., and Wehrmeister, H. L., Chem. Rev., 39, 269 (1946).
2. Fries, K., and Schurmann, G., Ber., 52, 2170 (1919).
3. Fries, K., Ber., 45, 2965 (1912).
4. Zincke, T., Ber., 44, 769 (1911).
5. Zincke, T., and Baeumer, J., Ann., 416, 86 (1918).
6. Lecher, H., and Wittwer, M., Ber., 55, 1474 (1922).
7. Lecher, H., and Holschneider, F., Ber., 57, 755 (1924).
8. Zincke, T., and Rose, H., Ann., 406, 103 (1914).
9. Lecher, H., Holschneider, F., Koberle, K., Speer, W., and Stocklin, P., Ber., 58, 409 (1925).
10. Zincke, T., and Farr, F., Ann., 391, 55 (1912).
11. Bohme, H., and Schneider, E., Ber., 76, 483 (1943).
12. Miller, C. J., and Smiles, S., J. Chem. Soc., 127, 224 (1925).
13. Billman, J. H., Garrison, J., Anderson, R., and Wolnak, B., J. Am. Chem. Soc., 63, 1920 (1941).
14. Billman, J. H., and O'Mahony, E., J. Am. Chem. Soc., 61, 2340 (1939).
15. Moore, M. L., and Johnson, T. B., J. Am. Chem. Soc., 57, 1517 (1935).
16. Moore, M. L., and Johnson, T. B., J. Am. Chem. Soc., 58, 1091 (1936).
17. Moore, M. L., and Johnson, T. B., Science, 81, 643 (1935).
18. Moore, M. L., and Johnson, T. B., J. Am. Chem. Soc., 57, 2234 (1935).
19. Moore, M. L., and Johnson, T. B., J. Am. Chem. Soc., 58, 1960 (1936).
20. Learmonth, E. K., and Smiles, S., J. Chem. Soc., 1936, 327.

Reported by R. S. Johnson
December 6, 1946

CHLOROALKYLSILANES

Recent developments in the chemistry of organic silicon compounds have dealt with chloroalkylsilanes, compounds which have one or more chlorine atoms in an alkyl group attached to silicon. The substitution of silicon for carbon in various organic halides causes them to undergo several new reactions, usually involving fission of the carbon-silicon bond. A study of the effect of structure on the reactivities of a number of these compounds has led to an increased understanding of the nature of the silicon atom in organic compounds.

1. Chloroalkylsilanes from alkyltrichlorosilanes.--Methyltrichlorosilane on chlorination gives Cl_3SiCH_2Cl, $Cl_3SiCHCl_2$ and Cl_3SiCCl_3 (1). Alkaline hydrolysis, with concentrated potassium hydroxide solution, in each case causes splitting of the carbon-silicon link. Sulfuryl chloride and benzoyl peroxide do not chlorinate methyltrichlorosilane; this is ascribed to the deactivating influence of the Cl_3Si- group on the α-hydrogen atoms (2a).

Chlorination of ethyltrichlorosilane by sulfuryl chloride gives a mixture of α- and β-chloroethyltrichlorosilanes, in the ratio 1:2.5. Dilute alkali attacks only the Si-Cl bonds of the former, but hydrolyzes the latter to silica and ethylene (2a).

$$C_2H_5SiCl_3 \xrightarrow[Bz_2O_2]{SO_2Cl_2} \begin{cases} CH_3CHClSiCl_3 \xrightarrow{OH^-} [CH_3CHClSiO_{1.5}]_x + 3\ Cl^- \\ + \\ ClCH_2CH_2SiCl_3 \xrightarrow{OH^-} C_2H_4 + SiO_2 + 4\ Cl^- \end{cases}$$

Similarly, α-chloroethyltrichlorosilane with methylmagnesium bromide gives α-chloroethyltrimethylsilane; the β-isomer forms tetramethylsilane and ethylene (2b). Heating a mixture of the two isomers with dry quinoline yields vinyltrichlorosilane and silicon tetrachloride (3).

N-propyltrichlorosilane affords a mixture of α-, β- and γ-monochloroalkylsilanes by treatment with sulfuryl chloride and benzoyl peroxide (2c). These give distinctive reactions with dilute alkali.

$$n\text{-}C_3H_7SiCl_3 \xrightarrow[Bz_2O_2]{SO_2Cl_2} \begin{cases} ClCH_2CH_2CH_2SiCl_3 \xrightarrow{OH^-} \text{△} + SiO_2 + 4\ Cl^- \\ + \\ CH_3CHClCH_2SiCl_3 \xrightarrow{OH^-} CH_3CH{=}CH_2 + SiO_2 + 4\ Cl^- \\ + \\ CH_3CH_2CHClSiCl_3 \xrightarrow{OH^-} [CH_3CH_2CHClSiO_{1.5}]_x + 3\ Cl^- \end{cases}$$

Alpha-chlorobenzyltrichlorosilane has been obtained similarly (2b); the chlorine atom attached to carbon is stable to dilute alkali.

2. Chloroalkylsilanes from dialkyldichlorosilanes.--From the chlorination products of dimethyldichlorosilane have been isolated $CH_3SiCl_2CH_2Cl$, $CH_3SiCl_2CHCl_2$ and $CH_3SiCl_2CCl_3$ (1). Hydrolysis of each compound by concentrated alkali results in the splitting of the C-Si bond characteristic of chloromethylchlorosilanes.

Chlorination of methylethyldichlorosilane attacks only the ethyl group, giving α- and β-chloroethylmethyldichlorosilanes (3). The former is dehydrochlorinated by quinoline to form vinylmethyldichlorosilane.

Treatment of the crude chlorination mixture of diethyldichlorosilane with quinoline yields vinyltrichlorosilane and divinyldichlorosilane (3).

3. Chloroalkylsilanes from trialkylhalosilanes.--Trimethylchlorosilane with chlorine gives $(CH_3)_2(CH_2Cl)SiCl$, $(CH_3)_2(CHCl_2)SiCl$ and $CH_3(CH_2Cl)_2SiCl$ (1). In general, a chloromethyl group attached to silicon is chlorinated in preference to an unsubstituted methyl group, as indicated by the relative yields of chloromethylchlorosilanes.

Reaction of triethylchlorosilane with sulfuryl chloride and benzoyl peroxide gives as before α- and β-chloroethyldiethylchlorosilanes (2d). The differences in reaction with dilute alkali between the side-chain chlorine atoms again appears.

$$(C_2H_5)_3SiCl \xrightarrow[Bz_2O_2]{SO_2Cl_2} (C_2H_5)_2(CH_3CHCl)SiCl + (C_2H_5)_2(ClCH_2CH_2)SiCl$$

$$(C_2H_5)_2(CH_3CHCl)SiCl \xrightarrow{OH^-} (C_2H_5)_2(CH_3CHCl)SiOH + Cl^-$$

$$(C_2H_5)_2(ClCH_2CH_2)SiCl \xrightarrow{OH^-} [(C_2H_5)_2SiO]_X + C_2H_4 + 2\,Cl^-$$

Only the chlorine attached to silicon in the α-isomer is alkylated by Grignard reagents.

Monochloro- derivatives of triethylfluorosilane have been prepared similarly (2d); they behave like those of triethylchlorosilane.

4. Chloroalkylsilanes from tetraalkylsilanes.--Photochemical chlorination of tetramethylsilane gives chloromethyltrimethylsilane (silico-neopentyl chloride) (2e). This compound reacts with potassium iodide in acetone solution to produce the correspondi

iodide; both halides form Grignard reagents. Silico-neopentyl chloride is about as reactive toward nucleophilic substitution reagents as n-hexyl chloride, but both the chloride and iodide are inert to silver nitrate.

Tetraethylsilane yields a mixture of α- and β-chloroethyltriethylsilanes with chlorine (4). Alcoholic sodium hydroxide in a sealed tube reacts with the former to produce vinyltriethylsilane.

The α-chloro- derivatives of tetraalkylsilanes are usually prepared by alkylating α-chloroalkylchlorosilanes with Grignard reagents. Some examples of these are:

$$Cl_3SiCH_2Cl \xrightarrow{3\ CH_3MgBr} (CH_3)_3SiCH_2Cl$$

$$CH_3CHClSiCl_3 \xrightarrow{3\ CH_3MgBr} CH_3CHClSi(CH_3)_3$$

$$(C_2H_5)_2(CH_3CHCl)SiCl \xrightarrow{CH_3MgBr} (C_2H_5)_2(CH_3CHCl)SiCH_3$$

The effect of various groups attached to silicon on the reactivity of α-chlorine atoms has been studied (2c, 2d). It was found that if aryl or alkyl groups were attached to silicon in the chloroalkylsilane, the reactivity toward nucleophilic substitution reagents was about as great as that of sec-butyl chloride. If one alkyl group were replaced by hydroxyl, or all three by chlorine, however, the reactivity was found to increase sharply. In no case did the α-chlorine atom react with silver nitrate solution.

The practical aspect of these investigations lies in their relation to the chemistry of the silicones. Since increasing chlorination of an alkyl group attached to silicon decreases its stability, chlorinated derivatives of the silicones will not be suitable as commercial polymers.

Bibliography

1. Krieble and Elliott, J. Am. Chem. Soc., 67, 1810 (1945).
2. Whitmore and co-workers, (a) J. Am. Chem. Soc., 68, 485 (1946); (b) ibid., 1083; (c) ibid., 488; (d) ibid., 1881; (e) ibid., 481; (f) ibid., 475; (g) ibid., 156; (h) ibid., 1380.
3. Hurd, J. Am. Chem. Soc., 67, 1813 (1945).
4. Ushakov and Itenberg, J. Gen. Chem. (U.S.S.R.), 7, 2495 (1937); C.A., 32, 2083 (1938).
5. Gilliam, Liebhafsky and Winslow, J. Am. Chem. Soc., 63, 801 (1941)
6. Patnode and Schmidt, J. Am. Chem. Soc., 67, 2272 (1945).
7. Sommer and Kerr, Abstracts of Papers of the Sept., 1946, Meeting of the Am. Chem. Soc.
8. L. H. Sommer, private communication.

Reported by H. K. Hall
December 6, 1946.

CATALYTIC AROMATIZATION

I. Introduction.--The term "catalytic aromatization" is a very broad one, but it will be limited here to apply only to the formation of aromatic compounds from paraffins or monoolefins. That specifically excludes the aromatization of cycloparaffins and of paraffins or olefins containing aromatic substituents.

II. Scope of the reaction.--Any paraffin or monoolefin containing six carbon atoms, at least five of which must lie in a straight chain, can be transformed into aromatic compounds in some degree. Cracking may occur before or after the aromatization process, but is only important in molecules containing more than eight carbon atoms. Isomerization may occur before or during the cyclization process. Table I has been compiled to illustrate the variety of hydrocarbons which have been aromatized successfully.

III. The catalyst.--From thermodynamic considerations Taylor and Turkevitch have deduced that the aromatization process must compete with a cracking reaction. Therefore a good aromatization catalyst must induce cyclization but must also restrict C-C bond rupture. The oxides of the metals of groups VI, V and IV are ideal for this purpose since at 450°C. they break the C-H but not the C-C bonds in hydrocarbons. Table II gives a list of some of the more active catalysts used for various aromatizations.

Since the catalysts rapidly lose their activity unless supported on some more stable material, the usual catalyst is supported on Al_2O_3, MgO or a purified clay. Certain inorganic substances such as CeO_2, K_2O and Sb_2O_4 have been used to promote the activity and prolong the life of the catalyst.

IV. Generalizations.--It has been stated by Hoog, Zuiderweg and Verheus that the main product of the aromatization of a compound which can yield several aromatic compounds will be the aromatic bearing the shortest possible side-chains.

According to Rideal it is necessary to revise the rule slightly. He says that in general the main product of such a reaction will be an aromatic compound with one methyl side chain and the remaining carbon atoms in excess of six in one normal chain.

V. Mechanisms.--That the monoolefin is an intermediate in the aromatization of a paraffin has been shown by Hoog, Zuiderweg and Verheus and also by Pitkethly and Steiner. The olefin is adsorbed on the catalyst where cyclization and dehydrogenation occur before desorption. Taylor believes that this is an oversimplification of the process which is a very complex one.

TABLE I

HYDROCARBON USED	% aromatics	The Aromatic products ident.
n-hexane	19.5	benzene
n-heptane	36	toluene
2-methyl hexane	31	toluene
n-octane	46	o-xylene
3-methyl heptane	35	p-xylene (55%), o-xylene (35%)
2,5-dimethyl hexane	52	p-xylene
n-nonane	58	o-methyl ethylbenzene
n-hexene-1	31	benzene
n-hexene-2	18	benzene
n-heptene-1	69	toluene
n-heptene-2	65	toluene
5-methylhexene-2	50	
2-methylpentene-2	32.5	
3-methylpentene-2	32	
2-ethylbutene-1	32	
3-ethyl hexane	--	ethylbenzene
2,3-dimethyl hexane	--	o-xylene(50%),p-xylene(10%)
decanes	--	naphthalene
2,3-dimethyl pentane	--	toluene
2,2,3-trimethyl pentane	--	m-xylene
2,2,4-trimethyl pentane	4-5	p-xylene
2-methyl-3-ethyl pentane	--	m-xylene(50%),o-xylene(25%) ethylbenzene, toluene
2,2-dimethyl hexane	18-20	m-xylene
3,3-dimethyl hexane	--	o-xylene(40%),m and p-xylenes
2,2-dimethyl heptane	ca. 40	

TABLE II

Catalysts and General Conditions

Catalyst	Temp.	Promotors used
Cr_2O_3 on Al_2O_3	450-550	K or Ce oxides
Cr_2O_3 on Al_2O_3	500	ZrO_2
MoO_2 on Al_2O_3	450-550	none
V_2O_5 on Al_2O_3	500-650	none
Heteropolyacids of Mo with V, Cr, Th, Fe, Al, Co	450-550	none
Pt on carbon	500-600	none

The assumption was made by Herington and Rideal that each hydrocarbon molecule is chemisorbed at two adjacent active centers on the catalyst surface, and that only certain adsorption positions can lead to cyclization. On this basis they have successfully calculated the yields of all the aromatics to be expected from the aromatization of a given hydrocarbon.

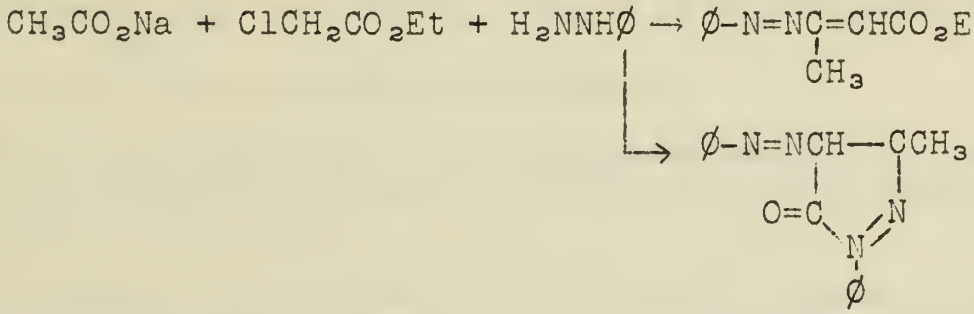
Bibliography

Turkevitch and Young, J. Am. Chem. Soc., 63, 519 (1941).
Komarewsky and Shand, ibid., 66, 1118 (1944).
Komarewsky and Riesz, ibid., 61, 2524 (1939).
Mattox, ibid., 66, 2059 (1944).
Oblad, Marschner and Heard, ibid., 62, 2066 (1940).
Green, J. Inst. Petroleum, 28, 179 (1942).
Archibald and Greensfelder, Ind. Eng. Chem., 37, 356 (1945).
Grosse, Mattox and Morrell, ibid., 32, 528 (1940).
Fischer, Watts, Harris and Hollenbach, ibid., 38, 61 (1946).
Fusteig, Refiner Nat. Gasoline Mfg., 17, 52, 168 (1938).
Hoog, Zuiderweg and Verheus, Trans. Faraday Soc., 35, 993 (1939).
Pitkethly and Steiner, ibid., 35, 979 (1939).
Taylor and Turkevitch, ibid., 35, 921 (1939).
Rideal, ibid., 35, 806 (1939).
Herington and Rideal, Proc. Roy. Soc., 184A, 434, 447 (1945).
Taylor, et al, J. Am. Chem. Soc., 61, 1766 (1939), ibid., 63, 1129, 1131, 1385, 1387, 2500 2801 (1941).

Reported by Elliot N. Marvell
December 13, 1946.

THE REACTION OF α-HALO KETONES WITH HYDRAZINE DERIVATIVES

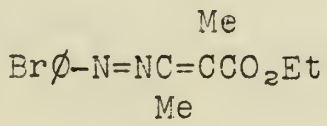
van Alphen found that ethyl α-chloroacetate reacted with phenylhydrazine in alcohol solution in the presence of sodium acetate to give a red crystalline precipitate of ethyl β-phenylazocrotonate (1). After long standing 1-phenyl-3-methyl-4-phenylazo-5-pyrazolone separated from the mother liquor. The question



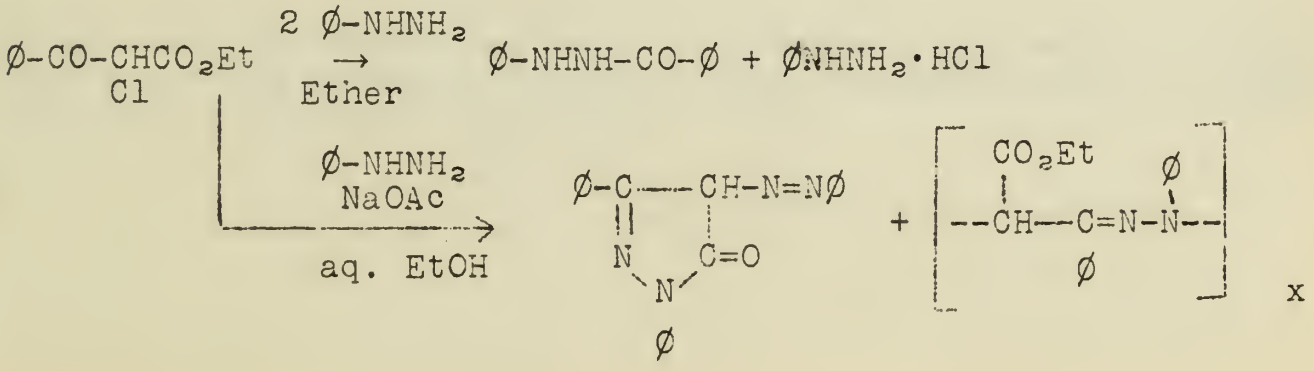
then arose whether other compounds with a halogen atom adjacent to a carbonyl group would also react with phenylhydrazine to give products with the conjugated system -N=N-C=C- (2).

Previous investigators had obtained products from phenylhydrazine and α-halocarbonyl compounds, but little was done concerning their structures (3,4).

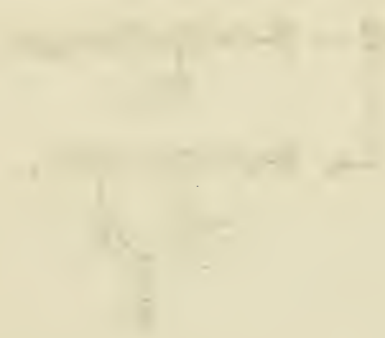
van Alphen found that α-chloro-α-methylacetoacetic ester reacts with p-bromophenylhydrazine to give crystalline β-(p-bromophenylazo)-α-methylethylcrotonate.



The reaction between phenylhydrazine and ethyl α-chlorobenzoylacetate gives different products according to the experimental conditions.



Substituted phenylhydrazines yielded resins with α-chlorobenzoylacetic esters.



Desyl chloride, Ø-CO-CHCl-Ø, was next examined. Resinous products were always obtained with phenylhydrazine or its substitution products. Thus it appears that an α-haloketone with the carbonyl group adjacent to a phenyl nucleus does not give a compound containing the grouping -N=N-C=C- when treated with phenylhydrazine.

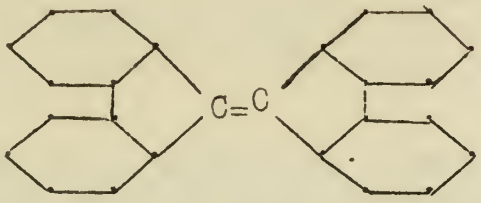
BrØ-N=NC=CH-Ø was obtained from the reaction of α-chloro-α-
$\quad\quad\quad

Bibliography

1. van Alphen, Rec. Trav. Chim., 64, 109, 305 (1945).
2. ibid., 65, 105 (1946).
3. G. Bender, Ber., 21, 2492 (1888).
4. Bodforss, Ber., 52, 1770 (1919).
5. van Alphen, loc. cit., 65, 109 (1946).
6. ibid., p. 112.
7. Hoogeveen, Rec. Trav. Chim., 50, 669 (1931).
8. Freer, Am. Chem. J., 21, 57 (1899).
9. Bodforss, loc. cit., 1769, 1773.
10. van Alphen, loc. cit., 65, 112 (1946).
11. Sidgwick, J. Chem. Soc., 1936, 535
12. Huckel, Z. Electrochem., 43, 752, 827 (1937).
13. Hess, Ann., 232, 234 (1885).

Reported by E. W. Nommensen
December 13, 1946.

Dibiphenylenethylene is a deep red solid melting at 187-189°C, and is one of the few colored hydrocarbons known. It was first prepared by De la Harpe and van Dorpe in 1875 (1).



DBPE (28,35) has been prepared in many different ways. The more important of these are listed below.

1. Harpe and Dorpe heated fluorene with lead oxide at elevated temperatures (1).

2. Fluorene treated at a temperature of 250-300°C with bromine or chlorine (3).

3. Fluorenone dichloride heated with copper powder in benzene (12,17) or metallic silver in ethyl acetate (14).

4. Dehydration of 9-hydroxydibiphenylenethane (15).

Sulfonation or nitration of dibiphenylenethylene leads to a partial ring substitution (19). The ring substituted compounds are usually prepared, however, from the substituted fluorenes or fluorenones. Only a few substituted dibiphenylenes are reported in the literature (10,18,23,26,34,22) even though a great variety of substituted fluorenes and fluorenones are known (32).

The red color of this hydrocarbon indicates that it has a special type of chromophore (6,7,8,21,19) since the corresponding tetraphenylethylene derivative is colorless and 9-methylene fluorene is also colorless. If the double bond in the 9,9'-position be saturated, by reduction with hydrogen or by addition of halogens the red color disappears. Dibiphenyleneallene and dibiphenylenebutadiene are also deeply colored.

The unique chemistry of this hydrocarbon is centered around the double bond in the 9,9' position. It is part of a crossed conjugated system. It has properties of an ethylenic isolated double bond but it also enters into reactions in which this double bond behaves as if it were conjugated with a carbonyl group. The reactions are listed below.

1. Reduction with zinc dust in acid solution or sodium metal in alcohol produces a saturated, colorless ethane derivative (1,3) zinc dust alone reduces it to fluorene.

2. Oxidation generally leads to fluorenone (2,3). It is not stable over a period of time in polar solvents and its use as an antioxidant has been cited in studies of the autoxidation of benzaldehyde (31).

3. Bromine and chlorine add quite readily to the double bond. The halogen atoms are readily removed with sodium or copper metal (17). The dibromide when heated with alcoholic potassium hydroxide regenerates the red hydrocarbon (4). The diacetate is also prepared from the dibromide (4).

4. Boiling DBPE with potassium hydroxide produces ortho-biphenylcarboxylic acid which on heating yields fluorenone (4).

7. Treating DBPE with nitric acid yields a bright yellow compound believed to be 9,9'-dinitrobiphenylenethane (4,19). This compound is quite easily decomposed to regenerate the hydrocarbon.

8. Sulfonylchloride yields the 9,9' dichlorocompound.

9. Phenyl lithium adds across the double bond. The lithium atom can then enter into various replacement reactions characteristic of organo metallic compounds (27).

10. DBPE can dehydrogenate certain organic compounds. For example 9-fluorenylamine is dehydrogenated in liquid ammonia to yield the imine. Pinck and Guido have recently compared the double bond in DBPE with the double bond α,β to a carbonyl group.

11. DBPE combines readily at room temperature in liquid ammonia with methyl amine, ethyl amine and dimethyl amine to give the 9-substituted ethane derivatives (28) ammonia and benzylamine react more slowly and secondary reactions take precedence. With diethylamine, triphenylamine or aniline no reaction takes place. This order of addition of these compounds corresponds to their order of addition to α,β unsaturated acids. This is the first instance that an amine has been added to an isolated double bond.

12. It has also been demonstrated that DBPE will undergo a Michael condensation readily with 2,7 dibromofluorene, 2,7,2',7', tetrabromodibiphenylenethene will also condense with fluorene itself (36). Here then is a Michael condensation where the labilizing groups are not the conventional ones (33).

BIBLIOGRAPHY

1. Harp, Van Dorp, W., Ber., 8, 1048 (1875)
2. Graebe, C., Ber., 25, 3146 (1892)
3. Graebe, C., Mantz, B., Ann., 290, 238 (1896)
4. Graebe, C., Stindt, H., Ann., 291, 1 (1896)
5. Klinger, H., Lonnes, C., Ber. 29, 2152 (1896)
6. Klinger, H., Lonnes, C., Ber. 29, 2157 (1896)
7. Smedley, I.; Chem. Soc., 87, 1254 (1905)
8. Hantzsch, A.; Glover, W., Ber. 39, 4157 (1906)
9. Manchof, W., Krische, P., Ann. 337, 198 ( )
10. Thiele, J., Wanscheidt, A., Ann., 376, 278 (1910)
11. Schmidt, J., Stutzel, H., Ann. 370, 1 (1909)
12. Schmidt, J., Wagner, H., Ber. 43, 1796 (1910)
13. Kliegl, A., Ber., 43, 2492 (1910)
14. Norris, J., Thomas, R., Brown, M., Ber 43, 2948 (1911)
15. Grignard, V., Conrtot, H., Compf. Rend., 152, 1493 (1911)
16. Staudinger, H., Kupfer, O., Ber. 44, 2208 (1911)
17. Schmidt, J., Wagner, H., Ann. 387, 157 (1912)
18. Gallas, G., Journ. Chem. Soc., 106, I, 1169 (1914)
19. Kehrman, F., Buffat, C., Helv. Chim. Act., 6, 955 (1923)
20. Courtot, Petitcolas; Compt. Rend., 180, 297 (1925)
21. Vanschaidt, A. A., C. A. 21, 580 (1927)
22. Vanschaidt, A. A., C. A. 21, 3617 (1927)
23. Korczynski, Karlowski, Kierzek; Bull. Soc. Chim. 41, 65 (1927)
24. Maitland, P., Tucker, S., Journ. Chem. Soc. 2559 (1929)
25. Pinck, L., Guido, H., Am. Chem. Soc. 54, 710 (1932)
26. Bergman, et al; Ber. 66 (B), 46, (1933)
27. Ziegler, K., Schafer, W., Ann., 511, 101 (1934)
28. Pinck, Guido; J. Chem. Soc., 57, 2398 (1935)
29. Hughes, E., Kuriyan, K., J. Chem. Soc. 1609 (1935)
30. France, H., Maitland, Tucker; J. Chem. Soc. 1739 (1937)
31. Wittig, G., Lange, W., Ann. 536, 266 (1938)
32. Rievesch, G., Ray F., Chem. Rev. 23, 287 (1938)
33. Taylor, R., Conner, R., J. Org. Chem., 6, 696 (1941)
34. Cardini, C.; C. A. 38, 1224 (1944)
35. Pinck and Guido; J. Amer. Chem. Soc., 68, 377 (1946)
36. Ibid., 68, 2014 (1946)

Presented December 20, 1946
Paul E. Hoch

THE THERMAL DECOMPOSITION OF SULFONIUM HYDROXIDES

Alkyl sulfonium hydroxides of the type R_3-S-OH (R's identical) decompose to give either R-OH or the corresponding olefin and water, in addition to R_2-S (1-5).

Primary alkyl sulfonium hydroxides of the types $(CH_3)_2$-$\overset{R}{\underset{|}{S}}$-OH and CH_3-$\overset{R_2}{\underset{|}{S}}$-OH (R's identical) generally decompose to give methyl alcohol and a sulfide containing the remaining two groups (4,6-9). However, if R is a secondary or tertiary alkyl group, the decomposition gives either R-OH or an olefin derived from R, in addition to a sulfide containing the remaining two groups (3,6,10).

Sulfonium hydroxides from which it is possible to split out two different olefins, i.e., sulfonium hydroxides containing at least two different alkyl groups larger than the methyl group, usually split out the smallest primary alkyl radical preferentially (4,6). However, also in this case, if a secondary group is present and also presumedly if a tertiary group is present, either of these will be eliminated in preference to a primary alkyl group (6).

Sulfonium hydroxides from which either an olefin or the corresponding alcohol is eliminated usually give the alcohol in dilute aqueous solution and the olefin in concentrated aqueous solution or aqueous alcohol solution (3,4,6,10).

Little is known about the decomposition of aryl sulfonium hydroxides (11). However, when the sulfur atom is in a ring, the corresponding methyl or ethyl sulfonium hydroxide usually decomposes to open the ring and give an unsaturated alkyl sulfide (12-17).

In general, the decomposition of sulfonium hydroxides is similar to the decomposition of quaternary ammonium hydroxides. The most notable difference being that sulfonium hydroxides with one or two methyl groups usually eliminate a methyl group as methyl alcohol while quaternary ammonium hydroxides with as many as three methyl groups seldom decompose in this manner.

Bibliography

1. Brown and Blaike, J. prakt. Chem., 23, 395 (1881).
2. Alvisi, Z. anorg. Chem., 14, 302 (1897).
3. Gleave, Hughes, and Ingold, J. Chem. Soc., 1935, 236.
4. Ingold and Kuriyan, J. Chem. Soc., 1933, 991.
5. Hass and Dougherty, J. Am. Chem. Soc., 65, 1238 (1943).
6. Ingold, Jessop, Kuriyan, and Mandour, J. Chem. Soc., 1933, 533.
7. Braun, Teuffert, and Weissbach, Ann., 472, 121 (1929).
8. Kehrman and Sava, Ber., 45, 2895 (1912).
9. Ingold and Jessop, J. Chem. Soc., 1930, 713.
10. Hughes and Ingold, J. Chem. Soc., 1933, 1571.
11. Dougherty and Hammond, J. Am. Chem. Soc., 61, 80 (1939).
12. Masson, J. Chem. Soc., 49, 233 (1886).
13. Mansfeld, Ber., 19 696, 2658 (1886).
14. Meyer, Ber., 19, 3262 (1886).
15. Demuth and Meyer, Ann., 240, 305 (1887).
16. Green and Sutherland, J. Chem. Soc., 99, 1174 (1911).
17. Grishkevich-Trokhimovskii, J. Russ. Phys. Chem. Soc., 48, 880 (1916).

Reported by J. H. Koehneke
December 20, 1946

FLUOROCARBONS

During the war the need arose for substances chemically inert against UF_6 and which could serve both as coolants and/or lubricants. Due to their extreme stability, certain fluorocarbons were found to fill these needs.

Methods of Synthesis

1. Older methods involve the use of KF, ZnF_2, SbF_3, SbF_5, HgF_2, AgF and HF on alkyl halides, olefins, and acetylenes. Alcohols have been used in some cases.

$$RX + MF \rightarrow RF + MX$$

$$RCH{=}CHR + HF \rightarrow RCHFCH_2R$$

$$R\text{-}C{\equiv}CH + HF \rightarrow R\text{-}CF = CH_2 \rightarrow R\text{-}CF_2\text{-}CH_3$$

In general, hydrogen atoms are not replaced and no more than two fluorine atoms can be placed on the same carbon if the adjoining carbon holds a halogen atom.

2. CoF_3, MnF_3, and AgF_2.

These fluorides contain metals in a very high oxidation state and are used to prepare perfluorocarbons, both in the aliphatic and aromatic series.

a. Fowler Method (CoF_3)

CoF_3 is prepared according to the equation

$$CoCl_2 + 2HF \xrightarrow{400^\circ} CoF_2 + 2HCl$$

$$2CoF_2 + F_2 \xrightarrow{300^\circ} 2CoF_3$$

The hydrocarbon is mixed with nitrogen and passed over a bed of CoF_3 at 300°. The degree of fluorination depends primarily on the rate of passage.

b. AgF_2, MnF_3, CeF_4, and PbF_4 have been successfully used in pilot-plant operation. The products vary only slightly. Difficulty in their preparation has limited their use.

3. Catalytic Fluorination (Columbia Method)

The improved technique of handling fluorine now makes its use feasible. The hydrocarbon and fluorine are diluted with nitrogen separately and gradually mixed at temperatures of 140°-325° in the presence of copper turnings coated with a thin layer of silver fluorides. Perfluorocarbons have been prepared by this method, although in low yields.

4. Introduction of Fluorine into an Aromatic Ring

Controlled fluorination of aromatic compounds is effected through the diazonium compound by the Schiemann method. The insoluable diazonium borofluoride is isolated, dried, and decomposed by heat to give the aryl fluoride.

Applications

1. CoF_3 and AgF_2 Methods.

Fowler and coworkers have prepared perfluorohexane, perfluoroheptane, perfluorocyclohexane, perfluoroethyl cyclopentane and others. Various oils have resulted from these fluorinations ranging from $C_{14}F_{30}$ to $C_{21}F_{44}$. Preparation of these fluorocarbons is entirely commercially feasible.

Complete fluorination of n-heptane gives, in addition to perfluoroheptane, low-boiling fluorocarbons, representing fragmentation, perfluoroethylcyclopentane and perfluoromethylcyclohexane, representing cyclization, and in addition some isomers of C_7F_{16} and small amounts of polymers.

By subjecting fluorochloroheptanes to AgF_2 or CoF_3 treatment, satisfactory fluorochlorocarbon coolants have been obtained.

Perhalogen olefins can be saturated with fluorine by use of these reagents. If the temperature is raised above 100°, perfluoro compounds result.

In the aromatic series, perfluorobenzene, perfluoronaphthalene, perfluorophenanthrene and others have been synthesized. McBee subjected hexachlorobenzene and pentachlorobenzotrifluoride to CoF_3 treatment and obtained perfluorobenzene and hexafluorotoluene respectively. Fluorination of hexafluoroxylene is accompanied by considerable cracking. o-hexafluoroxylene has not been completely fluorinated by any method.

In general, CoF_3 and AgF_2 completely fluorinate a hydrocarbon, effecting replacement of hydrogen and halogen and addition of fluorine to double bonds. The reaction is accompanied by varying amounts of fragmentation and polymerization.

2. Catalytic Methods.

Straight chain perfluorocarbons from C_4F_{10} to $C_{16}F_{34}$ have been prepared by use of fluorine and antimony fluorides. Naphthenic fluorocarbons and fluorocarbon lubricating oils have received extensive study. The products vary from gases to brittle, rosinlike solids depending on the reaction conditions.

Thompson directly fluorinated 4-chloro-1,3-bis (trifluoromethyl) benzene and isolated the following compounds representing all types of reactions:

a. Addition $C_6H_3ClF_2(CF_3)_2$ $C_6H_3ClF_4(CF_3)_2$

b. Addition and replacement $C_6H_3F_7(CF_3)_2$

c. Substitution, addition and replacement $C_6F_{10}(CF_3)_2$

d. Fragmentation $C_6F_{11}(CF_3)$ C_6F_{12}

e. Polymerization solid waxes

Catalytic fluorination generally results in low yields of the desired perfluorocarbon.

3. HF and SbF_3

HF in the presence of $SbCl_3$ or SbF_3, or HF at high temperatures in the absence of a catalyst, is used to effect replacement of halogen atoms and saturation of double bonds. Hexafluoroxylenes are synthesized in this manner. In only one instance has any replacement on an aromatic ring been observed. Trichloro-bis(trifluoro-methyl)benzene yields monofluorodichloro-bis(trifluoromethyl)benzene as one of several fluorination products. Tetrachlorophenylpentachloroethane gives only products where side-chain chlorines have been replaced.

Picolines, lutidines, and γ-collidines have been fluorinated by initial chlorination of the side-chains and subsequent replacement by fluorine. The products vary from one to nine fluorine atoms in the side-chain.

Properties

Perfluorocarbons range in physical properties from the previously known gases CF_4, C_2F_6, and C_3F_8 through liquid and solid perfluoroparaffins C_nF_{2n+2}, perfluoroolefins C_nF_{2n} and the isomeric perfluoronaphthenes boiling in the gasoline range, to perfluoro lubricating oils, greases and waxes.

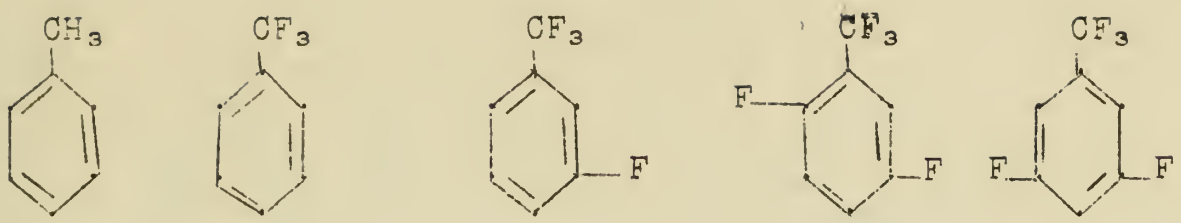
Despite their increased molecular weight, their boiling points approximate those of the parent hydrocarbons.

TABLE I

CH_4	-161°	CF_4	-128°	CCl_4	76°
C_2H_6	-88°	C_2F_6	-100°	C_2Cl_6	187°
C_2H_4	-104°	C_2F_4	-78°	C_2Cl_4	121°
C_4H_6	-3°	C_4F_6	6.6°		

In the aromatic series, the same general tendency is noted.

TABLE II



CH_3	CF_3	CF_3	CF_3	CF_3
		F	F F	F F
110.8°	102.3°	100.9°	107.8°	95°

Fluorocarbons are thermally stable. Many of them can be heated to 500° without cracking and they do not burn by themselves. They are inert toward even the most reactive chemical reagents. Fluorocarbon polymers are only slowly attacked by molten sodium at 100°. Even at 300°, acids and bases have no affect. That the carbon to fluorine bond is very stable, especially when several fluorine atoms are held by one carbon, is evidenced by the extreme exothermicity in the direct replacement of hydrogen by fluorine.

$$C_7H_{26} + 16F_2 \rightarrow C_7F_{26} + 16HF + 1630 \text{ K cal.}$$

Perfluoroolefins will add bromine and can be polymerized. Tetrafluoroethylene has been polymerized to give the extremely stable plastic Teflon.

Bibliography

(1) Abstracts of Papers, 110th Meeting, American Chemical Society (1946)
(2) Henne and Waalkes, J. Am. Chem. Soc., 68, 496 (1946)
(3) Renoll, ibid., 68, 1159 (1946)
(4) Brice, Pearlson, and Simms. ibid., 68, 968 (1946)
(5) Hanford and Joyce, ibid., 68, 2082 (1946)
(6) Henne, ibid., 67, 918 (1945)
(7) Finger, ibid., 66, 1972 (1944)

Reported by F. N. Baumgartner
January 3, 1947

EVIDENCE FOR A FREE RADICAL MECHANISM OF OXIDATION

Wieland (1) was the first to point out that a large number of oxidation reactions of organic compounds were hydrogen abstractions rather than oxygen additions. There now exists much evidence to show that the abstraction of hydrogen atoms from organic molecules is the initial step in oxidation and thus to support the concept that oxidation is a process of homolytic bond fission. This means that electron transfer is stepwise and consequently free radicals must occur as intermediates. The fact that many oxidations are chain reactions indicates that they are likely to be reactions of neutral radicals (2). It must be noted, however, that some oxidations, such as polar halogenation, are ionic displacements.

Autoxidation is definitely a free radical process. Ziegler (3) proved this in 1933 by showing that triphenyl methyl would initiate the chain autoxidation of aldehydes and olefins. He also pointed out that antioxidants were chain-breakers because of their easily available hydrogen atoms. He established the following reaction sequence for the autoxidation of benzaldehyde.

$$\phi_3C\text{-}C\phi_3 \rightleftarrows 2\phi_3C\cdot$$

$$\phi_3C\cdot + O_2 \rightarrow \phi_3C\text{-}O\text{-}O\cdot$$

$$\phi_3COO\cdot + \phi CHO \rightarrow \phi_3CCOH + \phi\dot{C}=O \qquad \text{Chain Starting}$$

$$\phi\dot{C}=O + O_2 \rightarrow \phi C(=O)\text{-}O\text{-}O\cdot$$

$$\phi C(=O)\text{-}O\text{-}O\cdot + \phi CHO \rightarrow \phi C(=O)\text{-}OOH + \phi\dot{C}=O \qquad \text{Reaction Chain}$$

Experimental evidence is steadily accumulating to show that the initial products of nearly all organic autoxidation reactions at moderate temperatures are hydroperoxides. The kinetics of autoxidation are complicated, but the fact that it is a chain reaction indicates the presence of free radicals. The thermal decomposition of the hydroperoxide may produce further radicals, which explains the autocatalytic nature of these reactions. In connection with the autoxidation of olefins, the recent demonstration of the α-methylenic activity of unsaturated substances is of especial theoretical significance. The fact that hydrogen abstraction from these compounds produces a resonance-stabilized free radical at least partially explains their susceptibility to oxygen attack in contrast to the inertness of the paraffins.

Diacyl and diaroyl peroxides, which decompose to give neutral radicals, can effect the direct oxidation of many organic compounds. The oxidation of acetic acid to succinic acid is a good example (4).

$$CH_3CO\text{-}C\text{-}O\text{-}COCH_3 \rightarrow 2CH_3CO\text{-}O\cdot$$

$$CH_3CO\text{-}O\cdot \rightarrow CH_3\cdot + CO_2$$

$$CH_3\cdot + CH_3COOH \rightarrow CH_4 + \cdot CH_2COOH$$

$$2\cdot CH_2COOH \rightarrow HOOC\text{-}CH_2\text{-}CH_2\text{-}COOH$$

Lead tetra-acetate is often employed in reactions of this type (5). It decomposes as follows:

$$Pb(OCOCH_3)_4 \rightarrow Pb(OCOCH_3)_2 + 2\cdot OCOCH_3$$

$$CH_3COO\cdot \rightarrow CH_3\cdot + CO_2$$

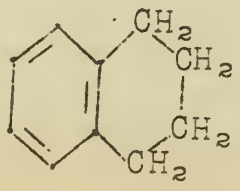
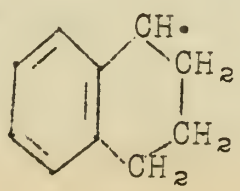
All the characteristic reactions of lead tetra-acetate can be explained by this free radical mechanism if it is remembered that both neutral acetate and neutral methyl radicals are produced in consecutive stages. The fission of α-glycols by lead tetra-acetate can be represented as a reaction of free acetate radicals, for it occurs without the evolution of CO_2.

$$\begin{matrix} R_2C\text{-}OH \\ | \\ R_2C\text{-}OH \end{matrix} + \cdot OCOCH_3 \rightleftarrows \begin{matrix} R_2C\text{-}O\cdot \\ | \\ R_2C\text{-}OH \end{matrix} + HOCOCH_3$$

$$2 \begin{matrix} R_2C\text{-}O\cdot \\ | \\ R_2C\text{-}OH \end{matrix} \rightleftarrows \begin{matrix} R_2C\text{-}OH \\ | \\ R_2C\text{-}OH \end{matrix} + \begin{matrix} R_2C\text{-}O\cdot \\ | \\ R_2C\text{-}O\cdot \end{matrix} \rightarrow 2R_2C = O$$

Reactions involving the dehydrogenation of alkyl groups, such as the conversion of acetic acid to succinic acid or the acetoxylation of toluene, more likely involve free methyl.

Waters has recently developed a technique (6) to show that many of the common oxidizing agents are capable of abstracting atomic hydrogen from organic molecules. This consists of demonstrating the catalytic action of these oxidizers on the autoxidation of tetralin, which requires the presence of α-tetralyl radicals. These reagents promote oxygen uptake by tetralin only when they are simultaneously reacting with tetralin itself.

$$Ox\cdot + \text{  } \rightarrow OxH + \text{  }$$

Initiates chain:

$$>CH\cdot + O_2 \rightarrow >CH-O-O\cdot$$

$$>CH-O-O\cdot + >CH_2 \rightarrow >CH-O-O-H + >CH\cdot$$

Many oxidizing agents have been tested and a surprisingly large number catalyze autoxidation. Some are inhibitors but this is also indicative of radical action.

Chromium trioxide and potassium permanganate are very effective autoxidation catalysts in homogeneous solution. In reactions with organic compounds, which have at most electron pair bonds, the reduction of Cr^6 to Cr^3 undoubtedly occurs in stages. It is convenient to represent it electronically as a three-fold repitition of the following equation.

$$\begin{matrix} O \\ \| \\ O \end{matrix}\!\!>\!Cr^6 = O + H-X \rightarrow \begin{matrix} O \\ \| \\ O \end{matrix}\!\!>\!Cr^5-O-H + X\cdot$$

Permanganate ion might act in a similar fashion, although a process involving both hydrogen abstraction and elimination of a hydroxyl radical is also possible.

The dehydrogenation of an organic compound by an oxide can only be represented by a one electron process if the oxidizing agent contains a double covalent bond.

Periodic acid, which like lead tetra-acetate, splits α-glycols is a positive autoxidation catalyst. Price and Knell (7) have suggested the intermediate formation of a cyclic periodate ester but atomic hydrogen abstraction by an I=O bond might also be postulated.

Osmium tetroxide, a selective reagent for the hydroxylation of olefinic bonds, also promotes the autoxidation of tetralin. The formation of a cyclic intermediate has been established by Criegee (8). Single electron processes of addition to olefins are familiar and the addition of one electron to an Os=O bond would be analogous to the addition of an H atom.

Quinones and disulfides have been employed for the dehydrogenation of hydrocarbons at high temperatures and they convert tetralin slowly to naphthalene. Criegee (9) has established the union of α-tetralyl and semi-quinone (radicals as an intermediate stage). In the case of disulfides, free mercaptide radicals can be produced by dissociation so the balance between positive and negative catalysis will depend on the relative rates of hydrogen abstraction and radical combination processes.

Dehydrogenation by sulphur or selenium may also proceed by an essentially similar mechansim.

To speculate more widely, free radical mechanisms may have a very extensive applicability in biological chemistry (10), for as Wieland emphasized most biological oxidations occur only in the presence of enzymes which have a dehydrogenase character. In these cases the co-enzyme plays the part of the generater of an active radical in a reaction chain, whereas the prosthetic group of the enzyme provides the initial free radical. In this connection it should be pointed out that free radicals do occur in the prosthetic groups of certain dehydrogenase enzymes. Also of significance is the fact that disulfide linkages are present in most enzyme proteins and our present evidence shows that thiol radicals, produced from the dissociation of disulfides, can abstract hydrogen atoms from other molecules.

Bibliography

1. Wieland, Ber., 55, 3639 (1922); J. Chem. Soc., 1931, 1055.
2. Waters, Trans. Far. Soc., 37, 779 (1941).
3. Ziegler and Ewald, Annalen, 504, 162 (1933).
4. Kharasch and Gladstone, J. Am. Chem. Soc., 65, 15 (1943).
5. Fieser, et al, J. Am. Chem. Soc., 64, 2043, 2052, 2060 (1942).
6. Waters, Trans. Far. Soc., 42, 184 (1946).
7. Price and Knell, J. Am. Chem. Soc., 64, 552 (1942).
8. Criegee, Annalen, 522, 75 (1936).
9. Criegee, Ber., 69, 2758 (1936).
10. Waters, J. Chem. Soc., 1946, 409.

Reported by Carl J. Claus
January 8, 1947.

ALKYL PEROXIDES

The simple alkyl peroxides constitute a class of compounds which have been extensively studied only recently. They promise to be useful as polymerization catalysts and Diesel oil addition agents as well as being of theoretical interest (1,2,3).

The compounds to be considered here are the hydroperoxides, the dialkyl peroxides and the peresters obtained from the former. Alkyl hydroperoxides and dialkyl peroxides may be synthesized as follows:

a. From dialkyl sulfates and hydrogen peroxide in the presence of alkalis. Early workers used this method to prepare methyl, ethyl and propyl compounds (4). A mixture of hydroperoxide and peroxide is usually obtained.

b. From hydrogen peroxide and a mixture of cold sulfuric acid and the alcohol. This modification of the older method has been developed recently by Milas and his coworkers (1,5,6,7). It is useful when the higher alkyl sulfates are not available and is well adapted for use in the preparation of mixed peroxides by substitution of an hydroperoxide for hydrogen peroxide.

c. From alkyl halides and alkali metal salts of hydroperoxides. This method has been patented by Dickey and Bell (2).

d. By air oxidation of aliphatic hydrocarbons at elevated tempera tures in the presence of hydrogen bromide. This procedure, patented by Vaughan and Rust, yields either hydroperoxides or peroxides, depending on the ratio of catalyst to hydrocarbon (3).

e. By air oxidation of hydrocarbons containing an active hydrogen atom. Hock and Lang, in studies on the autoxidation of hydrocarbons, have prepared a number of such hydroperoxides, usually from compounds with α-aryl substituents (8,9,10,11,12). This recalls the familiar behavior of tetralin which forms α-tetralone through an intermediate hydroperoxide.

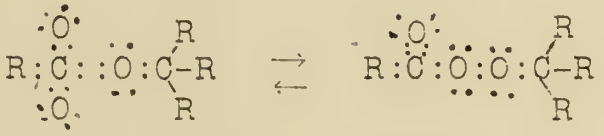
In their physical properties, the alkyl peroxides resemble alcohols and ethers (1,4). The lower homologues are extremely explosive, however, and must be distilled at reduced pressures. Increased size of the alkyl group increases the stability so that isopropyl hydroperoxide may be distilled at atmospheric pressure at 107°C without decomposition. In chemical reactions, hydroperoxides are weakly acidic, forming peresters and metal salts, and show a lowered oxidizing power compared to hydrogen peroxide. This effect is more pronounced in the higher homologues. In general, the more reactive compounds release iodine from iodides, give alcoholates with reducing metals and are hydrogenated to the alcohols. Palladium black releases oxygen as do the peroxidase enzymes.

Thermal decomposition of these compounds is of interest in connection with their activity as polymerization catalysts. The following scheme summarizes the decomposition of t-butyl hydroperoxide (1).

$$(CH_3)_3COOH \xrightarrow{250^\circ} (CH_3)_3CO\cdot + \cdot OH$$
$$\downarrow$$
$$CH_3COCH_3 + \cdot CH_3 \xrightarrow{+\,\rightarrow\, CH_3OH}$$

Acetone and methanol, together with small amounts of t-butyl alcohol and formaldehyde, were the compounds isolated. The low temperature decomposition, resembling that of hydrogen peroxide, gives t-butyl alcohol and oxygen which accounts for these latter substances. This free radical mechanism applies to compounds bearing larger groups, giving rise to radicals which may disproportionate to form olefins. If the alkyl substituents are not identical, it is the larger group which splits off preferentially. Dialkyl peroxides react similarly, giving the ketone and a hydrocarbon instead of an alcohol. Thus di-t-butyl peroxide gives acetone and ethane. The mechanism applies equally well in cases in which it would predict the scission of a ring; thus 1-methylcyclohexyl-1 t-butyl peroxide gives acetone, ethane, 3-methylheptanone-2 and 3,4-di-n-butyl hexanedione-2,5 (7). On the basis of this mechanism one would expect to obtain cyclohexan-1-ol-6-one from 1-decalin hydroperoxide. The intramolecular hemiacetal of this compound was actually isolated by Criegee (13).

Hydrogen peroxide presumably exists in a hybrid structure with linear and oxo-oxide contributions. The reactions of the peroxides indicate that both of these structures contribute, the free radical mechanism favoring the linear form and the release of oxygen supporting the oxo-oxide structure. By subtracting the molar refractivity of water from that of hydrogen peroxide, Milas and coworkers obtained the value 2.19 for the atomic refractivity of the peroxidic oxygen, a value close to that of the carbonyl oxygen (2.211) and far from that of the ether oxygen (1.643) (14). By subtracting the values for alcohols or ethers from those for hydroperoxides or dialkyl peroxides, corresponding values for the peroxide oxygen were obtained which agreed very well with the value above. Thus it is probable that no appreciable difference exists between the structure of hydrogen peroxide and that of an alkyl peroxide. Only with the peresters was the correlation poor. High values indicate that their structure must contain more than one peroxidic oxygen atom. Milas proposes the following structure containing two approximately equal oxygen atoms which is assumed to be in resonance with the normal structure.



Chemical evidence supports this structure in that peresters give high values for peroxidic oxygen in iodometric analysis.

Bibliography

1. Milas and Surgenor, J. Am. Chem. Soc., 68, 205 (1946).
2. Dickey and Bell, U. S. 2,403,709 (July 9, 1946).
3. Vaughan and Rust, U. S. 2,403,721 and 2,403,722 (July 9, 1946).
4. Rieche, Alkylperoxyde und Ozonide, Theodor Steinkopff (1931).
5. Milas and Harris, J. Am. Chem. Soc., 60, 2434 (1938).
6. Milas and Surgenor, ibid., 68, 643 (1946).
7. Milas and Perry, ibid., 68, 1938 (1946).
8. Hock and Lang, Ber., 76B, 167 (1943).
9. Hock and Lang, Ber., 77B, 257 (1944).
10. Hock and Lang, Ber., 76B, 1130 (1943).
11. Hock and Lang, Ber., 75B, 300 (1942).
12. Hock and Lang, Ber., 75B, 1051 (1942).
13. Criegee, Ber., 77B, 722 (1944).
14. Milas, Surgenor, and Perry, J. Am. Chem. Soc., 68, 1617 (1946).

Reported by V. R. Gaertner
January 10, 1947.

CATALYTIC ALKYLATION OF ISOPARAFFINS

The alkylation reaction, discovered in 1935 (23), represents the addition of fragments derived from an isoparaffin across an olefinic double bond. The reaction proceeds catalytically at low temperatures under the influence of such metal halides as boron trifluoride, aluminum chloride (23), concentrated sulfuric acid (2), anhydrous hydrofluoric acid (15,16). It can also be made to occur thermally, without a catalyst (14,31), or at lower temperatures in the presence of organic halides and nitro compounds (33, 36). At the peak of wartime production "alkylate" for 100:130 and 115:145 octane aviation fuel was produced at the rate of 9,400,000 tons per year (4).

A. SCOPE OF THE REACTION.

1. Paraffins.--Only isoparaffins are readily alkylated by all of the alkylation catalysts (11). Cyclohexane and propane can be alkylated with stronger catalysts (23,2), but methane, ethane (11) and neohexane (30) fail to react.

2. Olefins.--Ethene will alkylate isoparaffins with metal halide catalysts only (23,2). Propene requires a stronger catalyst or higher temperature than the butenes (2) all of which alkylate readily with all catalysts (2,23,15).

3. Catalysts.--Strongly acid substances, as aluminum chloride or 96-102% sulfuric acid, are the only substances with catalyze low temperature alkylation (11). Metal halides must be activated by traces of alcohol (40), water, or hydrogen halide (11).

4. Conditions.--The alkylation reaction is rapid and exothermic and requires refrigeration when aluminum chloride (23) or sulfuric acid is used as the catalyst (2). With anhydrous hydrogen fluoride the reaction proceeds best when the temperature is between 25-50°C (15). To prevent olefin polymerization, the latter is added slowly to a vigorously stirred suspension or emulsion of the catalyst in a large excess of the isoparaffin in the liquid phase (2).

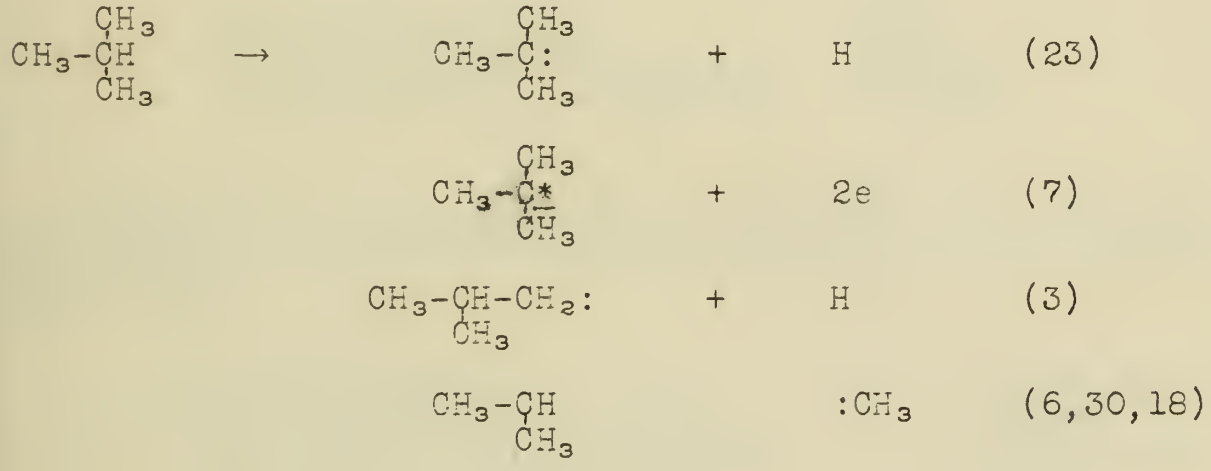
B. PRODUCTS.

When the reaction is carefully controlled, the main product consists of a simple mixture of a few isomeric paraffins corresponding to addition of the paraffin to the olefin. Varying amounts of both higher and lower molecular weight paraffins are obtained even when the reaction is run at low temperatures, as 20°C., and with a catalyst residence time of four or five minutes (18). Isomeric olefins yield different products (40). Catalyst residence time and thermodynamic functions of the product determine which of the mechanistically possible isomers predominate (6,18). Many isomers, thermodynamically more stable than the products (35), are formed in traces if at all, even with long catalyst residence time (18,17) (Tables I and II).

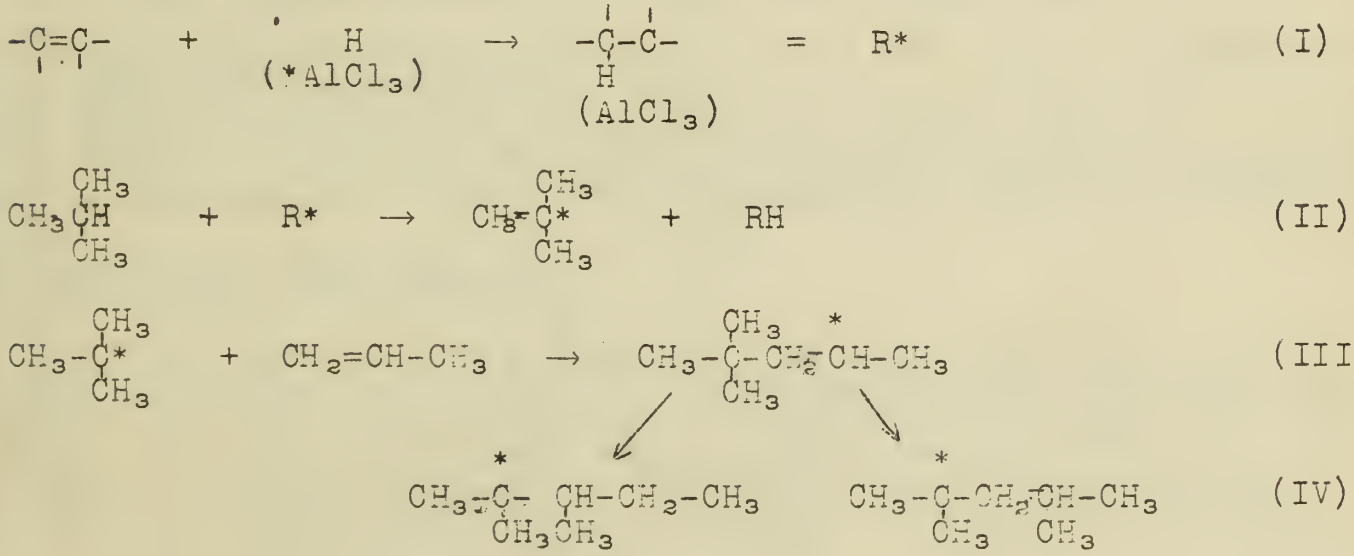
Gorin, Kuhn and Miles (18) distinguish (a) primary alkylation products, which decrease in amount with long catalyst residence time, and (b) secondary products, which increase in amount with long residence time (Table I). Increasing amounts of both higher and lower molecular weight paraffins are formed with increasing catalyst residence time (18).

C. MECHANISM.

All mechanisms proposed have been essentially ionic. The mechanism of isoparaffin activation has been formulated in the following different ways.



The most satisfactory mechanism appears to be that of Schmerling (37).



A carbonium ion is formed by reaction of the olefin with the catalyst (I). This abstracts a hydride ion from the isoparaffin (II) to form a new carbonium ion which adds to the olefin (III). The carbonium ion so formed isomerizes rapidly (IV) (7) according to the Whitmore theory of intramolecular rearrangement (43). De-

alkylation or further alkylation can also occur. The alkylate product is formed when the carbonium ion formed in (IV) abstracts a hydride ion from the isoparaffin (II). The reaction is thus seen as a chain reaction, with the catalyst acting merely to initiate the chains. Protonic activators are probably required to furnish the proton needed for reaction step (I).

The preliminary addition of a positive or acidic fragment to an olefin is the accepted basis of the following acid catalyzed reactions of olefins (28,29).

a. Polymerization	(44)
b. Depolymerization	(26)
c. Alkylation of Aromatics	(22,42)
d. Addition of Alkyl Halides	(38,41)

Reactions II, III, IV serve to integrate the alkylation reaction with other reactions of isoparaffins in the presence of strong acids.

a. Isomerization	(5,32,34,12)
b. Hydrogen-halogen exchange	(1,39)
c. Degradation and dealkylation	(19,25,45)
d. Alkylation of aromatics	(19)
e. Paraffin hydrogenation of olefins	(24,27)

This mechanism allows correlation of this reaction with:

a. The Lewis electronic concept of acids and bases as reactants (28) and catalysts (29).
b. DeWar's mechanism of addition to the double bond (9).
c. Ingold's electronic theory of organic reactions (21) especially as applied to substitution at a saturated carbon atom (10).

D. COROLLARY DEVELOPMENTS.

The industrial development of the alkylation reaction has stimulated the development of refined analytical techniques based on distillation and measurement of physical properties (17) Raman (20), infrared, ultraviolet and mass spectroscopy (8), and also chemical methods of analysis. Difficult engineering problems have been ingeniously solved (16,13,12). A potentially valuable reaction, the addition of alkyl halides to olefins, was developed by Schmerling (38,41) in his studies on the mechanism of this reaction.

TABLE I

Alkylation of Isobutane with HF or $AlBr_3$ Catalyst (18)
at -10°C.-+50°C.

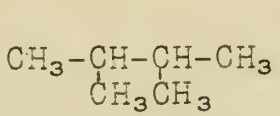
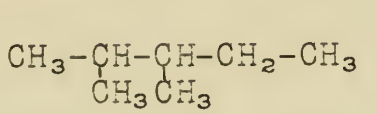
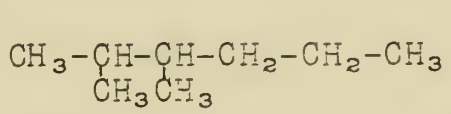
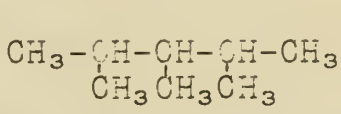
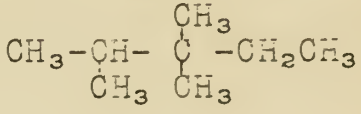
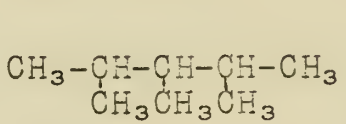
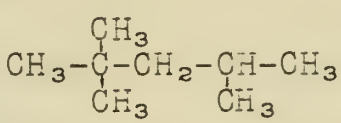
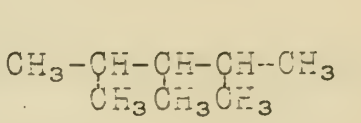
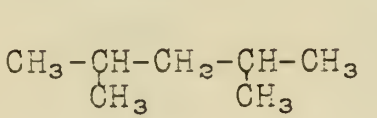
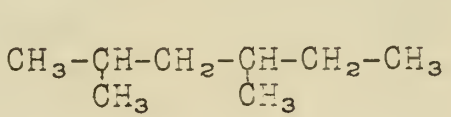
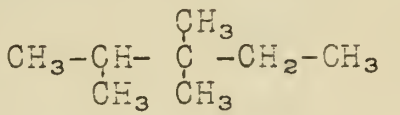
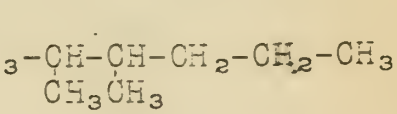
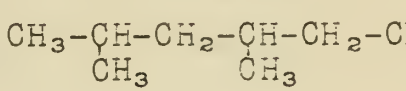
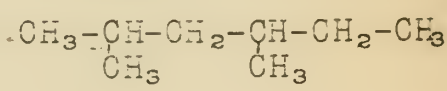
Olefin	Ethene	Propene	1-Butene	i-Butene	2-Butene
Primary Products					
					
Secondary Products					
					

TABLE II

Thermodynamic Equilibrium Percentages of Isomeric Octanes of Table I

Paraffin	2,4-Dimethyl Hexane	2,2,4-Trimethyl Pentane	2,3,4-Trimethyl Pentane	2,3-Dimethyl Hexane	2,3,3-Trimethyl Pentane
Theoretical at -10°C	52.0%	38.5%	3.6%	3.4%	2.5%
35) at -41°C	56.8%	29.6%	4.5%	5.7%	3.4%
Observed -10°C-+50°C	32-44%	32-40%	12-18%	6-12%	0-8%
18)					

TABLE III

Synthetic Isoparaffins Which Can Be Commerciall Prepared 90% Pure

Isoparaffin	Source			Octane #	
	Paraffin	Olefin	Method	ASTM	4 ml. TEL
$CH_3-\underset{CH_3}{CH}-CH_3$	n-Butane	-------	I and C		
$CH_3-\underset{CH_3}{CH}-CH_3-CH_3$	n-Pentane	------	I and C		
$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-CH_3$	i-Butane	Ethene	T. A.	93.4	111
$CH_3-CH_2-\underset{CH_3}{CH}-CH_2-CH_3$	n-Butane	Ethene	T. A.	74.3	96
$CH_3-CH_2-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-CH_3$	i-Pentane	Ethene	T. A.	84	98
$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2-CH_2-CH_3$	i-Butane	Propene	T. A.	93	100
$CH_3-\underset{CH_3CH_3}{\overset{CH_3}{C}}-CH-CH_3$	i-Butane	Propene	T. A.	102	113
$CH_3-\underset{CH_3}{CH}-CH_2-CH_2-CH_2-CH_3$	i-Butane	Propene	T. A.	45	73
$CH_3-\underset{CH_3CH_3}{CH}-CH-CH_3$	i-Butane	Propene	C. A.	94.3	111
$CH_3-\underset{CH_3CH_3}{CH}-CH-CH_2-CH_3$	i-Butane	Propene	C. A.	89	100
$CH_3-\underset{CH_3}{CH}-CH_2-\underset{CH_3}{CH}-CH_3$	i-Butane	Propene	C. A.	83.8	100
$CH_3-\underset{CH_3\quad CH_3}{\overset{CH_3}{C}}-CH-CH_3$	i-Butane	Butenes	C. A.	100	113.4
$CH_3-CH-\underset{CH_3\ CH_3}{\overset{CH_3}{C}}-CH_2-CH_3$	i-Butane	Butenes	C. A.	99.4	112
$CH_3-\underset{CH_3}{C}-CH_2-CH_2-\underset{CH_3}{CH}-CH_3$	i-Butane	i-Pentene	C. A.		
$CH_3-\underset{CH_3CH_3}{CH}-CH-CH_2-CH-CH_3$	i-Butane	i-Pentene	C. A.		
$CH_3-\underset{CH_3CH_3}{\overset{CH_3}{CH}}-CH-CH_2-CH_3$	--------	Butenes	H.C.D. hot acid	99.9	114
$CH_3-\underset{CH_3CH_3CH_3}{CH}-CH-CH-CH_3$	--------	Butenes	H.C.D. H PO	95.9	108

References: (12,13.17,31.33)

Key: I and C — Isomerization and /or cracking
T. A. — Thermal Alkylation
C. A. — Catalytic Alkylation
H.C.D. — Hydrocodimerization

Bibliography

1. Bartlett, Condon and Schneider, J. Am. Chem. Soc., 66, 1531-39 (1944).
2. Birch, et al., Ind. Eng. Chem., 31, 884-91, 1081-83 (1939).
3. Birch and Dunstan, Trans. Faraday Soc., 35, 1013-21 (1939).
4. Brown, Ind. Eng. Chem. (News Ed.) 24, 330-33 (1946).
5. Bloch, Pines and Schmerling, J. Am. Chem. Soc., 68, 153 (1946).
6. Caesar and Francis, Ind. Eng. Chem., 33, 1426-28 (1941).
7. Ciapetta, ibid., 37, 1210-16 (1945).
8. Coggleshall, Chem. Ind., 58, 256-59, 420-23 (1946); Russell and Coggleshall, ibid., 58, 586-89 (1946).
9. DeWar, J. Chem. Soc., 1946, 406-08.
10. Dostrovsky, Hughes and Ingold, ibid., 1946, 157-94.
11. Egloff and Hulla, Chem. Rev., 37, 323-99 (1945).
12. Evering, Fragen and Weems, Chem. Eng. News, 22, 1898-1902 (1944).
13. Field and Gould, Petr. Refiner, 25, 141-47 (1946).
14. Frey and Hepp, Ind. Eng. Chem., 28, 1439-45 (1936).
15. Frey, Chem. and Met. Engineering, 50, #11, 126-28 (1943).
16. Gerhold, Iverson, Nebeck and Newman, Trans. Am. Inst. Chem. Engrs., 39, 793-812 (1943).
17. Glasgow, Streif, Willingham and Rossini, Petr. Refiner, 25, 93-119 (1946).
18. Gorin, Kuhn and Miles, Ind. Eng. Chem., 38, 795-99 (1946).
19. Grosse and Ipatieff, J. Am. Chem. Soc., 57, 2415-19 (1935).
20. Grosse, Rosenbaum and Jacobson, Ind. Eng. Chem. (Anal. Ed.) 12, 191-94 (1940).
21. Ingold, Chem. Rev., 15, 235-74 (1934).
22. Ipatieff, Corson and Pines, J. Am. Chem. Soc., 58, 919-22 (1936)
23. Ipatieff, et al., J. Am. Chem. Soc., 57, 1616-21, 1722-24 (1935); 58, 913-15 (1936).
24. Ipatieff and Grosse, ibid., 58, 915-17 (1936).
25. Ipatieff, Komarewsky and Pines, ibid., 58, 918-19 (1936).
26. Ipatieff and Pines, ibid., 58, 1056 (1936).
27. Ipatieff and Pines, J. Org. Chem., 1, 464-89 (1936).
28. Luder, Chem. Rev., 27, 547-83 (1940).
29. Luder and Zuffanti, Chem. Rev., 34, 345-70 (1944).
30. McAllister, Anderson, Ballard and Ross, J. Org. Chem., 6, 647-68 (1941).
31. Oberfell and Frey, Refiner Natural Gas Mfr., 18, 486-93 (1939).
32. Oblad and Gorin, Ind. Eng. Chem., 38, 822 (1946).
33. O'Kelly and Sachanen, ibid., 38, 482-67 (1946).
34. Pines and Wackher, J. Am. Chem. Soc., 68, 595-99; 599-605 (1946)
35. Prosen, Pitzer and Rossini, RP1641, J. Res. Natl. Bur. Standards, 34, 225-61 (1945).
36. Sachanen and Caesar, Ind. Eng. Chem., 38, 43-45 (1946).
37. Schmerling, J. Am Chem. Soc., 66, 1422-23 (1944); 67, 1778-83 (1945).
38. Schmerling, ibid., 67, 1438-41 (1945).
39. Schmerling, ibid., 68, 195-96 (1946).

40. Schmerling, ibid., 68, 275-81 (1946).
41. Schmerling, ibid., 68, 1650-54; 1655-57 (1946).
42. Slanina, Sowa and Nieuwland, ibid., 57, 1547-49 (1935).
43. Whitmore, J. Am. Chem. Soc., 54, 3274-83 (1932).
44. Whitmore, Ind. Eng. Chem., 26, 94-95 (1934).
45. Whitmore and Johnson, J. Am. Chem. Soc., 63, 1481-82 (1941).

Reported by J. H. Brewster
January 10, 1946

SEMINAR TOPICS

II Semester 1946-47

A NEW NOTATION AND ENUMERATION SYSTEM FOR ORGANIC COMPOUNDS

G. Malcolm Dyson, Loughborough

The appearance of a new system of notation and enumeration for organic compounds devised by Dr. Dyson has excited much interest since it is applicable to very complicated molecules and is especially adapted for filing and entry upon punched cards.

The Geneva-Liege convention is entirely inadequate for complex molecules and the all too frequent coining of trivial names leads to confusion. Utilization of such a system as that to be discussed will certainly simplify library work and make possible several library operations which are now of prohibitive difficulty. Structural formulas are admittedly indispensable but they suffer from several disadvantages; no speech equivalent, large size, non-classifiability, and dependence upon the arrangement for rapidity of recognition.

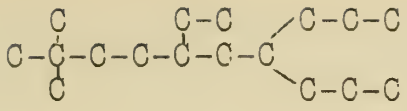
Dyson has applied his system to the entire Ring Index and to five volumes of Beilstein and has found that every entry gave a unique and unequivocal "cipher." The compound is expressed as a cipher composed of a linear series of symbols chosen from capital letters (except O), Θ, numerals, comma, stop (.), semicolon (;), the "en" rule (-), the stroke (/), parentheses (()), brackets ([]), and the sign of a series (...). No lower case letters, superscripts or subscripts are used. Thus, quinine is expressed as the following cipher.

K.ZN.4C[6AC6.1-4AC2.ZN.3C2.9E].6QC.11Q (1)

It will be noticed that the cipher is divided into sections by stops and each of these sections is an "operation." When a figure follows a letter without the interposition of any symbol, the figure is a "modulant." Figures preceding symbols indicate position and are termed "locants." The formation of a cipher consists in two steps; ciphering the basic carbon skeleton and ciphering the functional groups. It will be emphasized that the ordering of the cipher is of utmost importance for the best use of the system.

CIPHERING THE BASIC CARBON SKELETON.--

1. The letter C followed by a modulant (1 is understood) represents the longest carbon chain: dodecane is C12. Substituent alkyl groups are listed in order of decreasing size, using a fresh operation for each fragment size. Saturation is not indicated; rather, all unsaturation is described.



is C10.4C3.6C2.9,9C.

2. The letter A denotes ring structure; thus, cyclooctane is AC8. Adamantane is expressed as AC8.1-5,3-7AC. Different bridges are listed in decreasing order of carbon content.

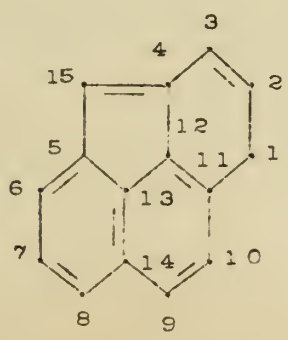
3. The letter E is used for unsaturation; C4.1,3E is butadiene. E1 and E2 denote cis- and trans- configurations respectively, and E3, a triple bond. It is to be noted that this system attaches generality to these prefixes which is not attained with present usage.

4. Six "conventional" rings are used as the basis for ciphering all aromatic and fused rings.

V is cyclopentadienyl	K is naphthalene
B is benzene	J is phenanthrene
W is indenyl	T is anthracene

Triethylbenzene would therefore be B.1,3,5C2. 1 as a sole locant is always omitted. The series sign is used for a "run" of similar substituents; pentamethylbenzene becomes B.1...5C. V and W rings are understood to be one hydrogen atom short in the cipher, with the location of the odd hydrogen shown by a modulant. Thus there are five indene operations: W1, W2, W4, W5, and W8. Modulated B's are used to indicate rings similar to benzene; cyclooctatetraene is B8. For odd numbered rings, a separate H operation is used to locate the odd hydrogen atom, and this operation is also used on hydrogenated aromatic rings. HK is decahydronaphthalene. Rules are made to cover choice of citing unsaturated cyclic compound. Citation of substituent rings is done in order of decreasing size.

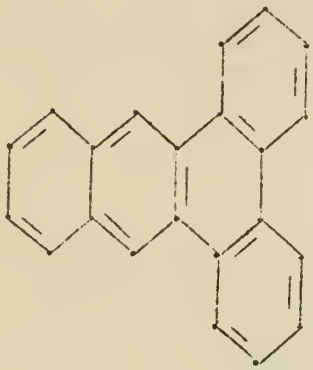
5. Fused rings are regarded as derived from the six rings of (4) above, the process being one of "annellation" to give "adducts." Rings are given seniority T, J, K, W, B, V, AC in cases of choice, and rings usually precede chains in the cipher.



J. 4-5B1.H

AC6.1-1AC4

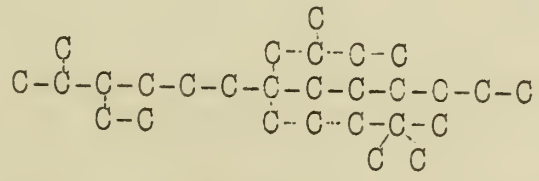
The frequent occurrence of certain higher fused ring systems has led to the assignment of 23 modulated forms of T, J. K, and W. For example, T3 is a T modulant referring to the ring below.



A large number of subsidiary rules deals with orders of preference for selecting ciphers for the ring systems.

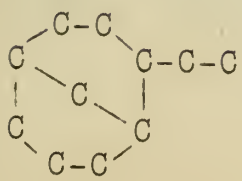
6. The Θ convention has the function of duplicating all which precedes it, and it is applied to chains of 20 or more carbon atoms and to certain symmetrical ring structures. Biphenyl is therefore B.Θ and sexiphenyl is B.Θ.4(4)22[B]. For chains with an odd number of carbon atoms, the odd atom is included in the Θ operation; e.g., heneicosane would be C10.Θ10-12C.

7. Enumeration follows the longest carbon chain in acyclic hydrocarbons, the numbering starting from the end which gives the lowest number to the second operation. The substituent chains are numbered consecutively after the stem itself in order of operation.

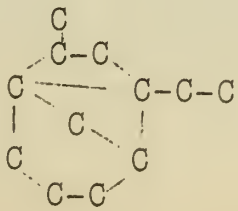


C13.7C5.7C4.3C2.2,17,17,20C

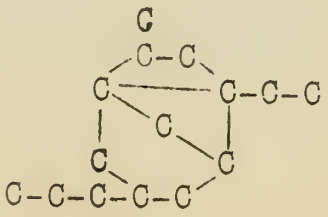
The rings below will exemplify usage with alicyclic compounds.



AC8.1-5AC.2C2



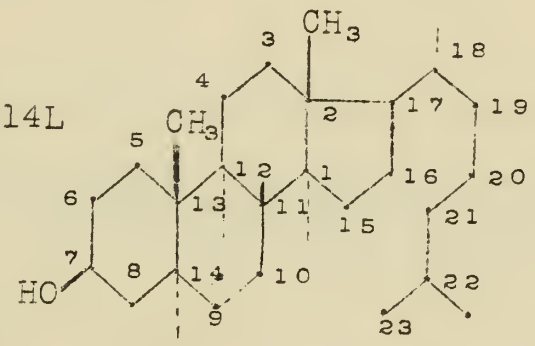
AC8.1-5AC.
1-4A.4C2.2C



AC8.1-5AC.1-4A
7C3.4C2.2C

The enumeration of aromatic rings follows an invariable pattern and all the atoms are given numbers. The use of brackets indicates that the cipher included has its independent numbering system, with the position of the bracketed substituent shown by locants before and after the first bracket. The stereochemical possibilities in hydrogenated fused rings systems are specified in an "L" operation; those bonds below the plane of the paper are specified. The formula and cipher for cholestanol are shown.

HJ8.17C6.2,13,18,22C.7Q.1,12,14L



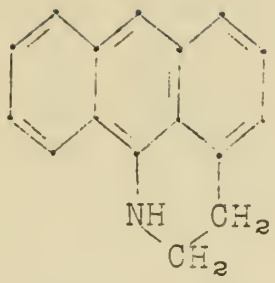
"R" can be used, if desirable, to indicate groups above the plane.

FUNCTIONAL GROUPS.--

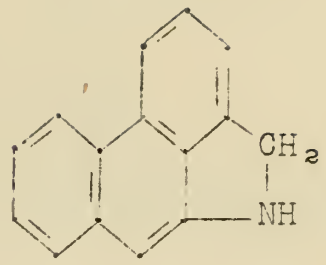
1. Oxygen functions:- Alcohols and phenols use Q. Ethers are cited as alkoxyl derivatives of the larger fragment,

C-C-C-O-C-C-C is C4.2C.4Q[C3]. For epoxides the operation AQ is used. The carbonyl group of aldehydes and ketones is represented by EQ; for quinones, it is easy to see that an HEQ cipher must be used. An X operation indicates a carboxyl group - citric acid is ciphered C5.3C.1,5,6X.3Q. The procedure for esters is similar to that for ethers: ethyl acetate and phenyl acetate are C2.X[C2] and B.[XC2], respectively. Triacetin is ciphered as C3.1,2,3[XC2]. For lactones A and X are conjoined. Peroxides and per acids require an additional Q, while the formulas for the molozonide and ozonide of pentene-2 are ciphered C5.2-3AQQYQ and AC5.1,2,4ZQ.3C2.5C, where Y signifies a dative bond.

2. Heterocyclic compounds:- As has been indicated in previous ciphers, Z is used for heterocyclic atoms, with the atom named in the same operation. Higher valences are shown by a modulant, and the order of citation is that of the periodic table. In adducts, ring fragments containing more than half carbon are ciphered as carbon adducts; otherwise, the adduct is ciphered by sequence.



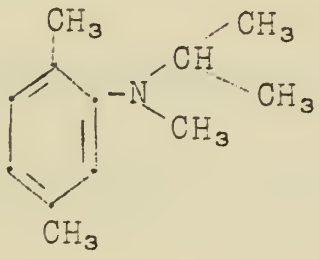
T.1-9AC3.17ZN



J.1-10ACN

Biotin is expressed as AC8.1-5A.3ZS.6,8ZN.2C5.13X.7EQ.

3. Nitrogenous functions:- Amines are ciphered with a simple N, while quaternary salts use N5 with the anion ciphered as attached to the nitrogen atom. B.1,4C.2NC2.9,10C represents



Amides follow the ester system, while other acid derivatives receive simpler treatment: COCl becomes EQCL, and anhydrides are named as derivatives of formic anhydride (CXCEQ) C5.2,2C.5N[EQC4]; is C-C-C-CONH-C-C-C-C-C. Nitroso, nitro and azide groups are ciphered N1, N2, and N3; and N4 refers to the azo groups both in rings and open chains. Thus the dye, 3,3'-dimethoxy-4,4'-bis(3"-naphthalenecarboxyanilide-1"-azo)-diphenyl is ciphered B.0.4,10N4 [K.3CEQN[B]].3,9QC. Hydroxylamines and oximes have no special operation, and hydrazines are ciphered as NN. Syn- and anti- configurations use the E1 and E2 operations. Other nitrogenous operations are shown below.

Benzonitrile	B.C.7E3N
Malonamidine	C3.1,3N,EN
Guanidine	CN,N,EN

4. Modulants of sulfur and phosphorous:- The table below shows the symbols for ciphering S and P compounds.

S	Divalent S	P	Trivalent P
S1	-SO-	P1	-PO
S2	$-SO_2-$	P2	$-PO_2$
S3	$-SO_3H$	P3	$-PO_3$
S4	quaternary S	P4	-P=P-
		P5	Pentavalent P
		ZP	Hetero-trivalent P

5. Other elements:- An "M" operation is used for other elements; e.g., $C_6H_5As(OH)_2$ is ciphered B.MAS.7,7Q.

6. Carbohydrates:- For rapid reference and indexing of saccharides, further abbreviations are utilized, and stereochemical points are shown by the "L" operation. D-Glucose is written G6.EQ.3L(open) or G6.1-5AQ.3L(pyranose). The Θ convention is used with polysaccharides.

For further examples, see the end of the following section.

GENERAL PRINCIPLES GOVERNING ENUMERATION AND CITATION.--

Enumeration follows citation in the cipher; each section of the cipher is enumerated in turn, sections in brackets being treated independently. The table below lists the order of procedure.

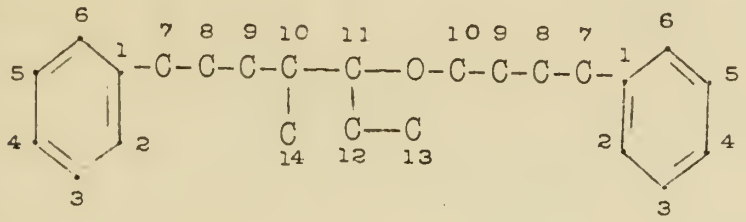
I. Primary Stem and Carbon Skeleton

1. The senior fused ring system with any adducts
   a. B or AC in order of decreasing size
   b. V and W before their modulated forms
   c. T and J modulants in order of decreasing size, lower modulant coming first
2. Heteroatoms in senior ring
3. Aryl or alkyl substituents in decreasing seniority
   a. When enumeration here is bracketed, the substituent's heteroatom is within the bracket
4. H and E operations in that order

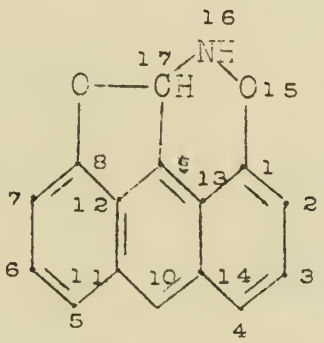
II. Functional Groups

5. Oxygen functions in the order AQCQ, AQ, ACX, AX, CXC, CX, XC, X, QC, Q, CEQ, HEQ, EQ, QQ
6. S, SE, TE operations
7. Nitrogenous functions
   a. Operations involving Q and N
   b. N,...N6, NN, EN, EN3
8. P, AS, SB, BI operations
9. Halogens; I, modulated I, BR, CL, F
10. M operations

For indexing, the above order is followed, except that H and E modifications follow functional variants.

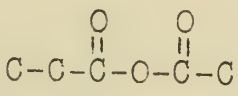


B.C7.10C.11Q[10B.C_4]

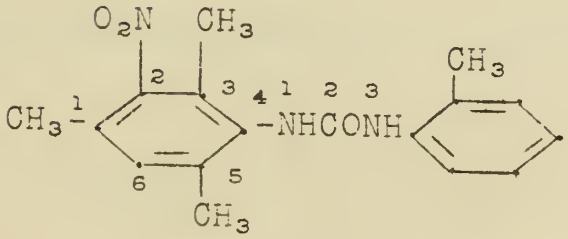


T.1-9AQNC.8-17AQ

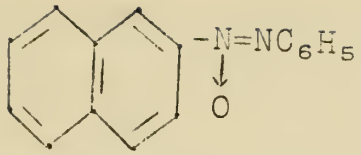
B.C.4NCC.7N[EQC3.2,2C]



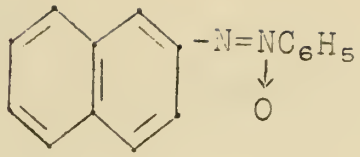
CXCEQ.C2.2C



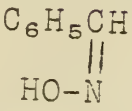
CEQ,N,N.[4B.1,3,5C.2N2].3[2B.C]



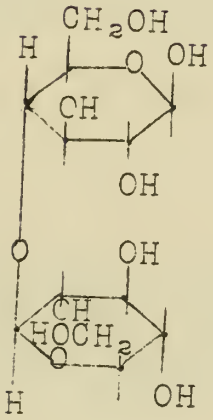
K.2YQN4[B]



K.2N4YQ[B]



B.CE1NQ

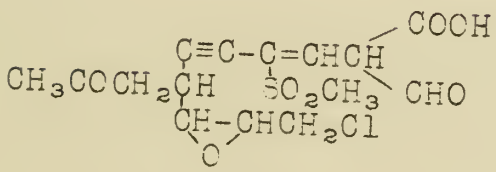


Cellobiose

[G6.1-5AQ.3L]θL;4

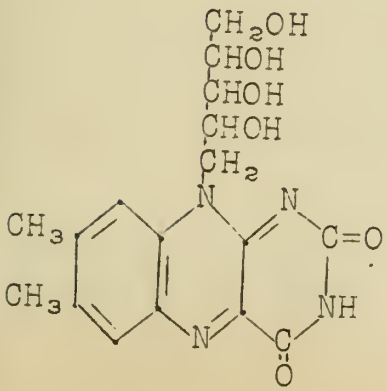
The semicolon shows loss of water.

Cellulose [G6.1-5AQ.3L][θL;4]n



Dr. Clarence Smith's "devised compound" J. Chem. Soc., 1072 (1936).

C1O.4C3.9C.7E.5E3.2.3EQ.1OX.12,14EQ.7S2[C].CL



Riboflavin

T.1,3,9,1OZN,9C5.6,7C.3,9H.16...19Q.2,4HEQ

MECHANICAL MANIPULATION OF CIPHERS.--

Dyson lists five ways in which his ciphers are amenable to mechanical handling.

1. Computation of molecular formula
2. Sorting of ciphers to order in indexing form
3. Production of printed ciphers
4. Searching through compounds for structural characteristics
5. Seaching for predetermined physical charactistic

To deal with operations (2) through (5), punched cards are used. Dyson has developed a system for an ordinary 80-hole punched card which leaves a residue for punching literature references or physical properties.

Bibliography

Dyson, "A New Notation and Enumeration System for Organic Compounds," Longmans, Green and Company, London.
(This seminar was prepared from a photographical reproduction of the proof of the book).

Reported by Ben F. Aycock, Jr.
February 7, 1947

THE *cis-trans* ISOMERISM OF POLYENE PIGMENTS

In a molecule containing a long conjugated system of unsymmetrically substituted double bonds, a large number of stereoisomers are theoretically possible, involving various combinations of *cis* and *trans* configurations around these bonds. Until fairly recently, however, investigations into the occurrence of *cis-trans* isomerism have been confined to molecules containing only a few double bonds.

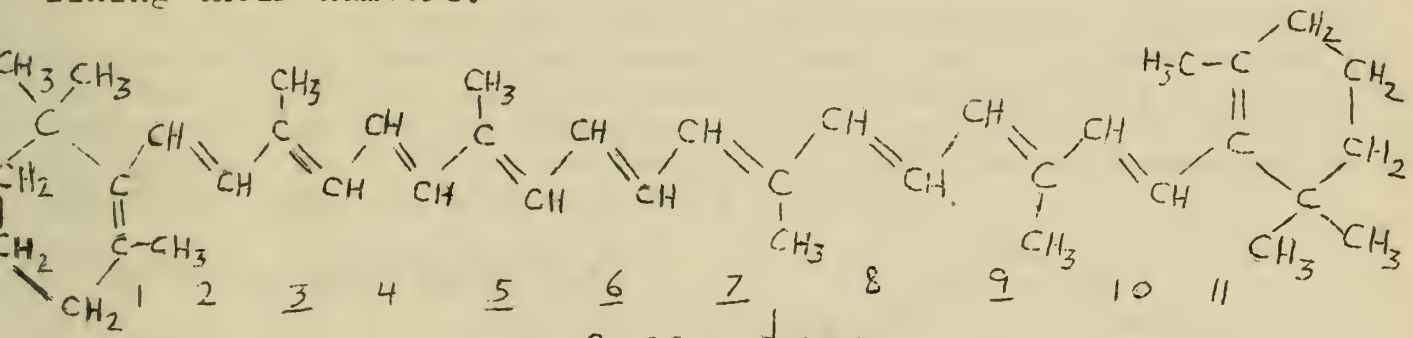
The carotenoids are among the most readily available and thoroughly investigated compounds containing such a long conjugated system. This group includes a number of natural plant and animal pigments, with the characteristic type of carbon skeleton and double bond system shown in the formula for β-carotene on page ?. Members of the series vary in the nature of the groups terminating the molecule, which may be cyclic or acyclic, in the length of the unsaturated chromophore, and in the presence or absence of oxygen in the terminal groups. In addition, certain natural pigments of lower molecular weight, apparently formed from the C_{40} carotenoids by oxidative elimination of the end groups, are included in the class. In general, the natural pigments have the all-*trans* configuration, as shown for β-carotene.

The first suggestion of a *cis* configuration in such a molecule occurred when Herzig and Faltis (1) isolated an isomer of natural bixin. They ascribed this, however, to a shift in the position of a double bond. Karrer and his co-workers (2) and Kuhn and Winterstein (3) indicated that the isomers were of the *cis-trans* type, and that the conversion of the labile to the stable form could be brought about by iodine catalysis. Similar results were reported in the cases of crocetin.

The extension to the C_{40} carotenoids was based on the observation of Gillam and El Ridi (4) that both α- and β-carotene, upon being chromatographed on an alumina column, gave rise to isomeric products, adsorbed below the natural pigment on the column. They considered that the isomerism was produced by the chromatographic procedure, and discussed both *cis-trans* shifts and shifts in the position of a double bond to explain their results.

Zechmesiter and his co-workers have investigated this phenomenon at great length. For references a review by Zechmeister may be consulted (5). They demonstrated that the isomerization was not produced by chromatographing, but was the result of a slow thermal isomerization of the pigments on standing in solution. In all the pigments investigated a short period of refluxing of the solutions produced isomers which could be separated by chromatography. These were characterized by a shift in the position of the visible absorption maximum to shorter wave-lengths, and a diminution in the intensity of absorption. Iodine was also employed as a catalyst for these isomerizations, and they were shown to be entirely reversible.

Mulliken (6) and Pauling (7) showed that these optical changes were those to be expected following a trans → cis shift. Pauling simplified the problem, when he pointed out steric reasons for concluding that only certain bonds in the long polyene chain could be expected to exist in a cis configuration. In the formula of β-carotene shown the double bonds of the chromophore are numbered; the stereochemically effective ones are indicated by underlining their numbers.



β-carotene

This decreases the number of isomers expected, although the number is still large, ranging from 20 in β-carotene to 128 in lycoxanthin. An argument was also presented correlating the magnitude of the shift in the absorption maximum with the number of trans → cis changes which had occurred.

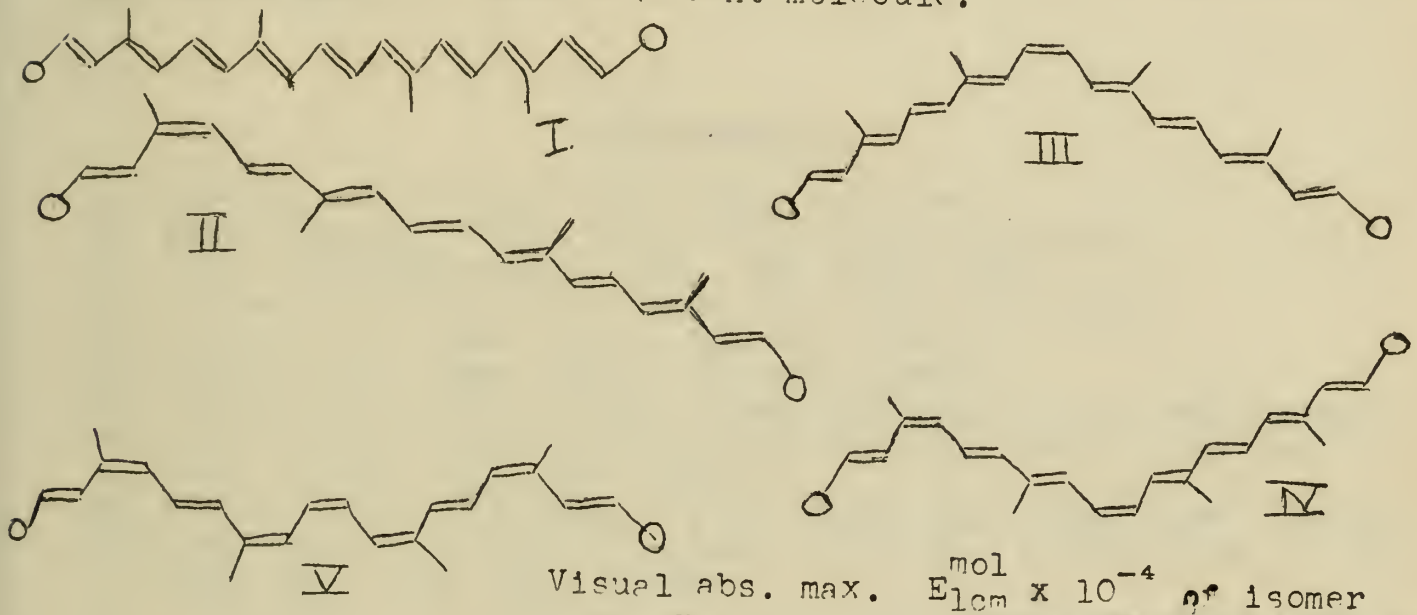
The discovery of a naturally occurring partially cis isomer of lycopene (8) was followed by the discovery of a similar isomer of α-carotene. These were at first assumed to be all cis (in the restricted sense indicated above) on the basis of the spectral shift; this was later modified when it was found they could be converted to pigments with their absorption maxima at still shorter wave-lengths. Using these compounds as the basis for further isomerization experiments the number of characterized isomers in a given stereoisomeric set was increased; ten out of the sixty-four predicted isomers of lycopene were described.

In addition to the methods of iodine catalysis and thermal isomerization in solution already described, several new methods were introduced. These included melting of the crystalline materials in an inert atmosphere, shaking of the solutions with strong acid, and exposure of the solutions to sunlight (insolation).

The use of spectral curves for characterization of members of some sets led Zechmeister and Polgar (9) to the discovery of an important phenomenon, the so-called cis peak. Upon treatment of a natural all trans carotenoid with iodine a new absorption band in the region from 320-380 mμ was observed. The various isomers produced contributed unequally to the effect. Pauling (10) furnished a theoretical interpretation of the effect, suggesting that molecules with a cis double bond in the central part of the chromophore should show a high cis peak, while molecules with several cis double bonds would not show one.

By the use of the postulates that the shift in the absorption maximum was proportional to the number of double bonds in the cis configuration, that the appearance of a cis peak denoted a bent molecule, and that thermal isomerism would be expected to affect the central portion of the chromophore especially strongly, Zechmeister and his group were enabled to tentatively identify several members out of each set investigated.

In the case of methyl bixin five isomers were isolated, four in crystalline form. They were assigned the structures shown in outline form below, on the basis of the spectral data given in the table, and the thermal interconversions indicated. In addition the all cis methyl bixin is indicated, to show that an accumulation of cis bonds does not produce a bent molecule.



	Visual abs. max. $m\mu$	$E^{mol}_{1cm} \times 10^{-4}$ of isomer - value of all-trans	M.P.
Natural methyl bixin	485	0.4	198°
All trans methyl bixin	490	---	161
Neomethylbixin A	485	2.8	191
Neomethylbixin C	479.5	1.4	151

Natural compd. II → Neo C IV
2-cis methyl bixin ← 2,5-dicis methyl bixin
↑ ⋮
⋮ ↓
All trans compd. I → Neo A III
← 5-cis methyl bixin

V is all cis compound, not known.

(Heavy arrows indicate easy thermal transformations, dotted transformations that do not take place to a great extent.)

In collaboration with Le Rosen (11), Zechmeister extended this treatment to the case of the diphenyl polyenes. Synthetic all *trans* diphenyloctatetraene was isomerized to yield a mixture of the all *trans*, the 2-*cis*, and the 2,3-di*cis* isomers. The 1- and 4-double bonds did not assume the *cis* configuration, due to the steric effect of the benzene ring.

The great importance of physical methods of analysis and the theoretical interpretation of the data obtained should be emphasized. The use of chromatography for the separation of isomers and the establishment of identity between isomers stable only in solution, and the employment of the iodine equilibrium curve to characterize the various members of a stereoisomeric set was indispensable.

Bibliography

1. Hertzig and Faltis, Ann., 431, 40 (1923).
2. Karrer *et al.*, Helv. chim. Acta, 12, 741 (1929).
3. Kuhn and Winterstein, Ber., 66, 209 (1933).
4. Gillam and El Ridi, Biochem. J., 30, 1735 (1936).
5. Zechmeister, Chem. Rev., 34, 267 (1944).
6. Mulliken, J. Chem. Phys., 7, 364 (1939).
7. Pauling, Fortschr. Chem. organ. Naturstoffe, 3, 203 (1939).
8. Zechmesiter, LeRosen, Went, and Pauling, Proc. Nat. Acad. Sci. (U. S.), 27, 468 (1941).
9. Zechmesiter and Polgar, J. Am. Chem. Soc., 65, 1522 (1943).
10. Zechmesiter, LeRosen, Schroeder, Polgar, and Pauling, J. Am. Chem. Soc., 65, 1940 (1943).
11. Zechmesiter and LeRosen, J. Am. Chem. Soc., 64, 2755 (1942).

Reported by A. E. Senear
February 14, 1947

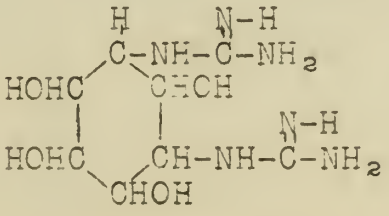
THE CHEMISTRY OF STREPTOMYCIN

I. Introduction.--Streptomycin is an antibiotic substance first discovered by Waksman and coworkers in 1944 (1) in filtrates of cultures of an actinomycete, Streptomyces griseus. Streptomycin (2,3,4,5), whose molecular formula is $C_{21}H_{39}N_7O_{12}$, is a strongly basic compound which forms salts of several types, reacts with carbonyl reagents and upon hydrogenation, takes up one mol of hydrogen to form dihydrostreptomycin (13,18). Whereas streptomycin is inactivated by carbonyl reagents, dihydrostreptomycin is not. Treatment with methanolic hydrochloric acid (6) breaks down streptomycin, giving two products, one a strongly basic guanido compound, and the other a nitrogen-containing disaccharide.

II. Streptidine.--The strongly basic guanido compound derived from the degradation of streptomycin was named streptidine (7,8,9, 10,12) and was found to have the formula $C_8H_{18}N_6O_4$. Streptidine gives a positive Sakaguchi reaction showing the presence of guanido groups and gives no nitrogen in the Van Slyke test showing that it has no primary amino groups. Oxidation with permanganate yields two mols of guanidine so that there must be two guanido groups in the molecule. Formation of an octaacetate shows that there must also be four hydroxyl groups since mono-substituted guanidines form diacetates.

When streptidine is hydrolyzed with alkali, ammonia and carbon dioxide are given off and streptamine, $C_6H_{14}N_2O_4$, is formed. Streptamine shows two primary amino groups in the VanSlyke test. It forms hexaacetyl and hexabenzoyl compounds from which N,N'-diacetyl and N,N'-dibenzoyl derivatives can be prepared. Oxidation of streptamine with periodic acid shows that it has a cyclic structure.

Oxidation of streptidine with periodic acid indicates that the guanido groups must be either in 1,3- or 1,4-positions. Proof of the actual positions is shown in two ways. Pyrolysis of hexaacetylstreptamine yields 2,4-diacetamidophenol. Oxidation of N,N'-dibenzoylstreptamine with periodic acid followed by oxidation with bromine water produces a dibenzoylaminoglutaric acid which would not be formed if the amino groups in streptamine were 1,4-. Thus, the amino groups in streptamine and therefore, the guanido groups in streptidine, are 1,3-. Streptidine then is 1,3-diguanido-2,4,5,6-tetrahydroxycyclohexane.



Streptidine

III. Streptobiosamine.--When streptomycin is treated with methanolic hydrochloric acid, one of the products is a derivative of a nitrogen-containing disaccharide, which disaccharide was named streptobiosamine (6). The derivative obtained in the above mentioned reaction was methyl streptobiosaminide dimethyl acetal. Acid hydrolysis of methyl streptobiosaminide dimethyl acetal followed by acetylation yields as one product, a pentaacetylhexosamine.

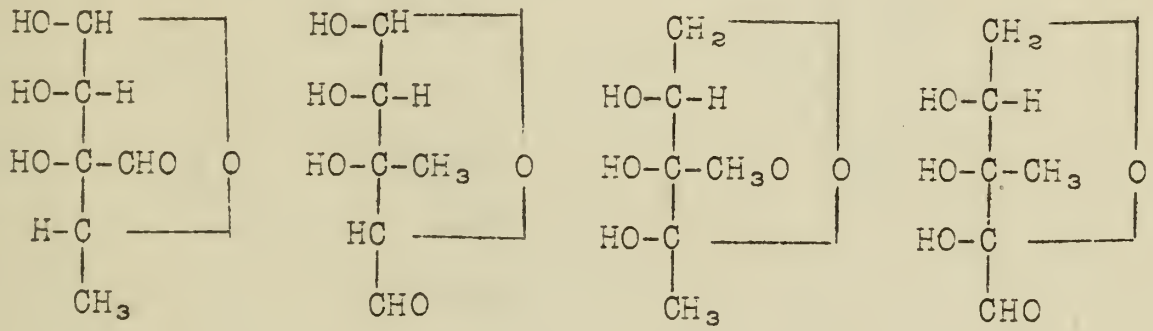
A. N-Methyl-l-glucosamine (11).--Hydrolysis of the pentaacetylhexosamine yields a hexosamine which gives l-glucose phenylosazone on treatment with phenyl hydrazine. Oxidation of the hexosamine with mercuric oxide gives an acid which has the same melting point as N-methyl-d-gluccsamic acid but opposite optical rotation. The acid synthesized starting with l-arabinose, methylamine and hydrogen cyanide (Strecker reaction) proved to be identica with the one obtained by mercuric oxide oxidation of the hexosamine derived from streptobiosamine. Conversion of the synthetic acid to the lactone, reduction of the lactone and acetylation of this product gives a pentaacetylhexosamine identical with that derived from the hydrolytic products of streptobiosamine. Therefore, N-methyl-l-glucosamine is one of the parts of streptobiosamine.

B. Streptose.--Knowing the molecular formulas of streptomycin, streptidine and N-methyl-l-glucosamine, it can be calculated that the second half of the disaccharide should have a formula $C_6H_{10}O_5$. This compound was named streptose (streptonose). However, in all attempts to isolate streptose from the hydrolytic products of streptobiosamine derivatives, it is found that the streptose has decomposed during hydrolysis. The structure of streptose then is shown indirectly by reactions of its derivatives.

Since streptomycin reacts very readily with carbonyl reagents (6,20,21), apparently there is a free carbonyl group somewhere in the molecule. In dihydrostreptomycin this carbonyl group has been reduced and since both streptidine and N-methyl-l-glucosamine can be isolated from hydrolytic products of dihydrostreptomycin, the carbonyl group in streptomycin must be located in the streptose portion of the molecule. If methyl streptobiosaminide dimethyl acetal is acetylated, a tetraacetyl derivative is obtained. A Zerewitinoff determination (16) shows that there is a hydroxyl group in this molecule that is resistant to acetylation. Presumably, this would be a tertiary hydroxyl. Treatment of this tetraacetyl derivative with ethyl mercaptan gives ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal (14). If this mercaptal is treated with fresh Raney nickel, each of the ethyl mercapto groups is replaced by hydrogen, giving tetraacetylbisdesoxystreptobiosamine. This may be converted to N-acetylbisdesoxystreptobiosamine which shows no reducing action. Hydrolysis of this N-acetyl derivative gives bisdesoxystreptose and N-methyl-l-glucosamine showing that the linkage of the two parts of streptobiosamine involves the number one carbon of N-methyl-l-glucosamine.

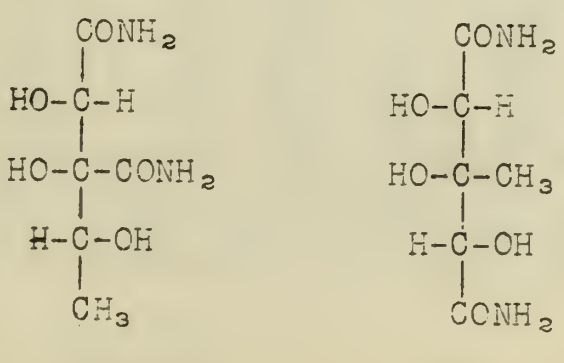
Bisdesoxystreptose (15) has the molecular formula $C_6H_{12}O_3$. It forms a bis-p-nitrobenzoate and reacts with one mol of periodate giving a product which, after hydrolysis, yields osazones of diacetyl upon treatment with excess phenyl hydrazines. Reaction with boric acid gives an acidic complex showing that the hydroxyl groups are cis. Bisdeoxystreptose then is 3,4-dimethyl-2,4-dihydroxytetrahydrofuran.

From the above data then, it can be seen that there are four possible structures for streptose.

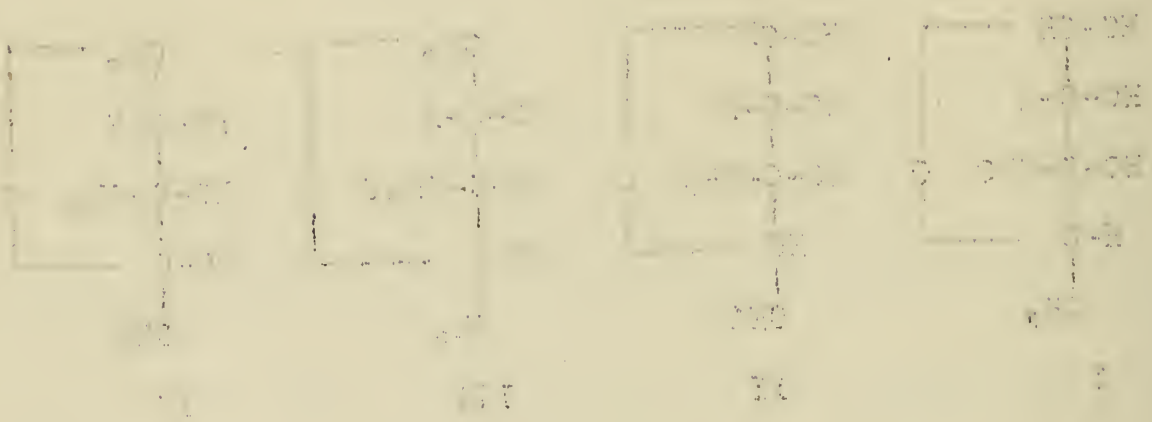


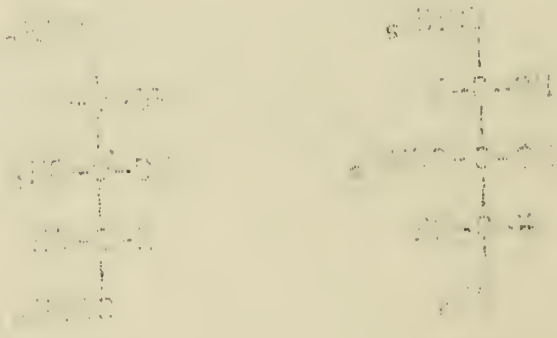
I II III IV

Treatment of ethyl tetraacetylthiostreptobiosaminide diethyl mercaptal with mercuric chloride and cadmium carbonate (17) removes the ethyl mercapto groups giving tetraacetylstreptobiosamine. Oxidation of this product with bromine water, followed by acetylation, gives pentaacetylstreptobiosamic acid lactone. This acid lactone can be hydrolyzed to give streptosonic acid lactone and N-methyl-l-glucosamine. Streptosonic acid lactone has the formula $C_6H_8O_6$. Structures III and IV for streptose are thus eliminated since they would not give six-carbon dibasic acids. Since a Kuhn-Roth oxidation shows one $C\text{-}CH_3$ in the acid lactone, a straight chain structure for it is eliminated. From the acid lactone, streptosonic acid diamide may be prepared for which there are two possible structures.

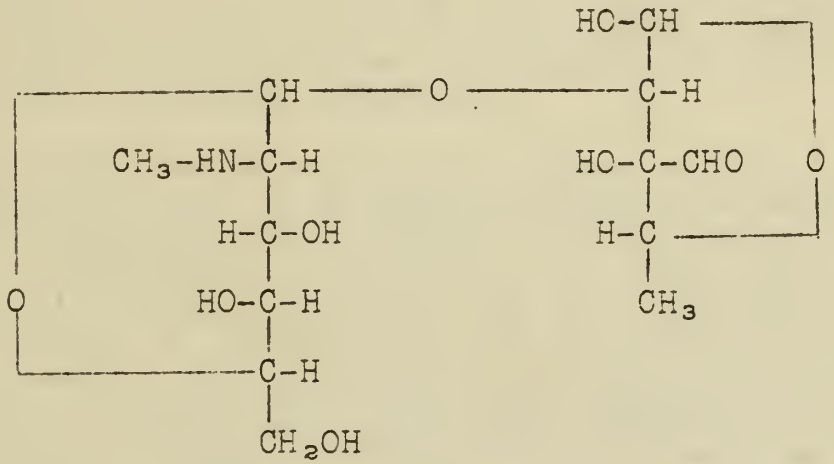


I II





This diamide used two mols of periodate on oxidation showing that there are three adjacent hydroxyl groups. No volatile acid was produced showing that structure II for the diamide is not correct since it would yield acetic acid. Streptosonic acid lactone reacts with two mols of periodate giving glyoxalic acid, oxalic acid and acetaldehyde, further proof for structure I of the diamide and therefore, structure I of strepose.



The complete structure for streptomycin can not be written as yet since the position of the linkage of streptobiosamine to streptidine is still unknown.

Bibliography

1. Waksman, et al., Proc. Soc. Exptl. Biol. Med., 55, 61 (1944).
2. Carter, et al., J. Biol. Chem., 160, 337 (1945).
3. Folkers, et al., J. Am. Chem. Soc., 68, 1460 (1946).
4. Folkers, et al., Science, 102, 34 (1945).
5. Folkers, et al., J. Am. Chem. Soc., 67, 1866 (1945).
6. Folkers, et al., Science, 102, 506 (1945).
7. Carter, et al., Science, 103, 53 (1946).
8. Carter, et al., Science, 103, 540 (1946).
9. Fried and Wintersteiner, J. Biol. Chem., 162, 391 (1946).
10. Folkers, et al., J. Am. Chem. Soc., 68, 29 (1946).
11. Folkers, et al., J. Am. Chem. Soc., 68, 536 (1946).
12. Folkers, et al., J. Am. Chem. Soc., 68, 776 (1946).
13. Folkers, et al., J. Am. Chem. Soc., 68, 1390 (1946).
14. Folkers, et al., J. Am. Chem. Soc., 68, 2096 (1946).
15. Folkers, et al., J. Am. Chem. Soc., 68, 2405 (1946).
16. Folkers, et al., J. Am. Chem. Soc., 68, 2557 (1946).
17. Folkers, et al., J. Am. Chem. Soc., 68, 2679 (1946).
18. Fried and Wintersteiner, J. Am. Chem. Soc., 69, 79 (1947).
19. Schenck and Spielman, J. Am. Chem. Soc., 67, 2276 (1945).
20. Bartz, et al., J. Am. Chem. Soc., 68, 2163 (1946).
21. Donovick, Rake and Fried, J. Biol. Chem., 164, 173 (1946).

Reported by R. L. McGeachin
February 14, 1947

SODIUM REDUCTION OF FATTY ACID ESTERS

The reduction of esters to alcohols by means of sodium and a reducing alcohol is commonly known as the Bouveault-Blanc method from the men who discovered the reaction in 1903 (1,2). They carried out the reduction by the addition of sodium in large pieces to the ester dissolved in absolute ethanol. This method, which uses a large excess of sodium and alcohol, has proved very convenient in synthetic organic research and is still a recommended procedure (3). However, this method has several disadvantages as a commercial preparation of alcohols. A considerable amount of sodium is consumed by reaction with the reducing alcohol, ethanol is required in large amounts and is not easily recovered as absolute ethanol, and the temperature of boiling ethanol is somewhat low for rapid and efficient reduction.

Since the method of Bouveault and Blanc was introduced, several modifications have been made which have recently led to a process of vast commercial importance. It was found (4) that the efficiency of sodium could be increased and the reaction time shortened from six hours to one hour by the addition of a mixture of ester and ethanol to the molten sodium suspended in toluene. Later by using sodium sand in toluene to prevent an initial reaction delay (5,6), the reaction time was decreased to 4-5 minutes with better yields. Butanol (7) was found to have an advantage over ethanol since it could be obtained in a more anhydrous condition. During the war large quantities of fats were reduced by sodium to the alcohols and glycerol. A report (8) on this process shows it to be a commercial application of the above modifications.

Hydrogen formed by the direct reaction of alcohols with sodium plays no role in this type reduction (9). Baeyer (1892) considered that the dissolving metal reacted with the solvent to liberate hydrogen atoms and that these "nascent" hydrogen atoms then reduced the organic compound before they could combine with each other to form molecular hydrogen. Until recent years this theory was widely accepted and is still used by many authors (10,11). The overall ester reduction can be represented by a simple equation using ethyl palmitate, sodium, and ethanol.

$$C_{15}H_{31}CO_2Et + 4Na + 2EtOH \rightarrow C_{15}H_{31}CH_2OH + 4EtONa$$

The most commonly accepted mechanism (8,12) explains the reduction by a series of reactions.

$$RC(=O)-OR' + 2Na \rightarrow RC(ONa)(Na)-OR' \xrightarrow{R''OH} RC(ONa)(H)-OR' \rightarrow RC(Na)(H)=O \xrightarrow{2Na} RC(Na)(H)-ONa \rightarrow$$

$$\xrightarrow{R''OH} RCH_2ONa$$

Hydrolysis of the sodium alcoholate mixture with water yields the free alcohols. Any direct reaction of sodium with the reducing alcohol is a side reaction.

$$R''OH + Na \rightarrow R''ONa + 1/2H_2$$

These equations show that the theoretical ratio of raw materials is 1 mole of ester, 2 moles of reducing alcohol and 4 atoms of sodium, but when the reduction is run with ethanol in this ratio there is sufficient direct reaction with sodium to upset this ratio. A desirable reducing alcohol would thus be one which will react with the sodium ketal but not appreciably with the sodium under the reaction conditions. It was found (8) that the half-life periods of alcohols in the presence of sodium under these conditions was 2-4 minutes for primary alcohols of lower molecular weight, 10-15 minutes for secondary alcohols, and over 20 minutes for tertiary alcohols. Tertiary alcohols are found in some cases to decompose the intermediate sodium ketals too slowly while secondary alcohols have about the proper reactivity. The choice of a particular alcohol depends on availability, cost, ease of recovery in anhydrous condition, and solubility of the sodium alkoxide under actual reduction conditions. Methyl hexalin, the isomeric mixture of o-, m-, p-hexahydrocresols, methyl isobutyl carbinol, and tertiary-butanol are examples of alcohols which have been used.

Toluene or xylene is the preferred solvent except in a few special cases. It is convenient to choose a solvent such that the heat of reaction can be removed by allowing the solvent to reflux in a very efficient metal condenser. In practice about 5 per cent excess of sodium with little or no solvent is placed in the reaction flask. Ester to be reduced is mixed with about 5 per cent excess of the reducing alcohol and enough solvent to keep the reaction mixture fluid during the reduction. The ester mixture is run in as rapidly as possible into the reaction flask containing the stirred molten sodium. The reduction mixture must not be allowed to come in contact with air since it will ignite spontaneously at that temperature. This is prevented by solvent vapors.

The reaction mixture must be kept fluid since gelling isolates the sodium globules and prevents complete reaction. Glycerides give more fluid mixtures than do methyl esters, other factors being equal. Methyl isobutyl carbinol is an excellent reducing alcohol since it gives much more fluid mixtures than most other alcohols. After the reaction is finished the product with any excess sodium is run directly under an actively boiling aqueous solution. In this way the sodium alcoholates and sodium are decomposed under a steam cover and without fire hazards. If any large lumps of sodium are present they are removed mechanically. The solvent and reducing alcohol are collected together from the steam distillate and the water content lowered to 0.05% by azeotropic distillation in the case of a xylene-methyl isobutyl carbinol mixture, and the mixture is ready for reuse. The efficiency of the reaction can be studied by the amount of hydrogen liberated and may be improved considerably by this study. Yields of the alcohols range from 70-96 per cent based on the esters.

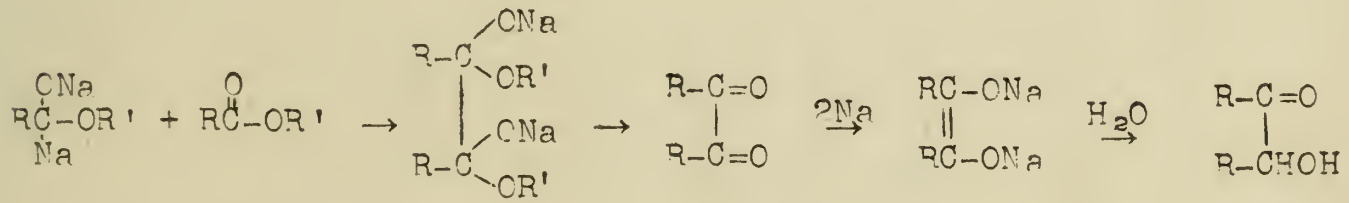
Saturated alcohols, and to a limited extent unsaturated alcohols, can also be prepared by catalytic reductions (13). High temperatures and pressures are required for the reduction and under

these conditions glycerol is reduced to propylene glycol. In the sodium reduction method, the glycerol is easily recovered as well as sodium hydroxide. Reduction of unsaturated esters to the corresponding alcohols is not commercially feasible catalytically since the zinc chromite catalyst must be used to the extent of about half the weight of the ester.

Reductions by means of sodium becomes more attractive as the molecular weight of the parent ester increases. Unsaturated esters with an average of five ethylenic bonds (not conjugated) can be reduced with little effect on the degree of unsaturation, as in the case of menhaden oil. In the reduction of linoleic ester, it was reported (14,15,16) that in addition to linoleyl alcohol, the conjugated alcohol of the same unsaturation was formed due to a shift of the ethylenic bond by the strong alkali. This ethylenic shift was not mentioned in the industrial report (8) on the reduction of this ester. Eleostearic acid, the glyceride of which amounts to over 85 per cent of tung oil, contains three conjugated double bonds. On reduction, an alcohol is obtained with two double bonds which are not conjugated, an isomer of linoleyl alcohol.

All saturated fatty acid esters have been reduced in good yield by this method to the corresponding alcohol. Unsaturated alcohols such as linoleyl, linolenyl, oleyl, clupanodonyl, ricinoleyl, erucyl, and abietyl alcohols have also been prepared in good yields by this method.

Reducing alcohols which are too low in reactivity to alcoholize the intermediate sodium ketals with sufficient speed give bimolecular reaction products or acyloins. The effect is the same to some extent as if all the reducing alcohol were omitted. This reduction requires only half the sodium needed to produce a higher alcohol. In the absence of a reducing alcohol the sodium ester ketal enters into a Grignard type reaction with a second ester molecule (8,12).



The preparation (17) of acyloins has been extended from 12 carbons to 36 carbons by the sodium reduction of fatty acid esters in the same way as described above with the exclusion of the reducing alcohol.

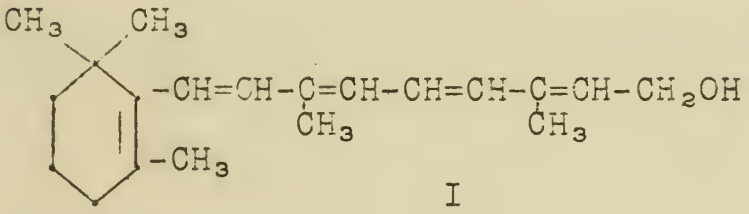
Bibliography

1. Bouveault and Blanc, Compt. rend., 136, 1676 (1903).
2. Bouveault and Blanc, Bull. soc. chim., 3, 31, 666 (1904).
3. Blatt, Organic Syntheses, Vol, II, p. 154 (1943).
4. Levene and Allen, J. Biol. Chem., 27, 433 (1916).
5. Adams and Marvel, Organic Chemical Reagents IV, pp. 50-56 (1922).
6. Marvel and Tanenbaum, J. Am. Chem. Soc., 44, 2645 (1922).
7. Blatt, Organic Syntheses, Vol. II, p. 372 (1943).
8. Hansley, Ind. Eng. Chem., 39, 55 (1947).
9. Campbell and Campbell, Chem. Rev., 31, 77 (1942).
10. Anglaret and Palfray, Compt. rend., 223, 205 (1946).
11. Palfray and Anglaret, Compt. rend., 223, 860 (1946).
12. Kharasch, Sternfeld, and Mayo, J. Org. Chem., 5, 362 (1940).
13. Sauer and Adkins, J. Am. Chem. Soc., 59, 1 (1937).
14. Turpeninen, J. Am. Chem. Soc., 60, 56 (1938).
15. Kass and Miller, J. Am. Chem. Soc., 61, 482 (1939).
16. Kass and Burr, J. Am. Chem. Soc., 62, 1796 (1940).
17. Hansley, J. Am. Chem. Soc., 57, 2303 (1935).

Reported by Rayner S. Johnson
February 21, 1947

THE SYNTHESIS OF VITAMIN A

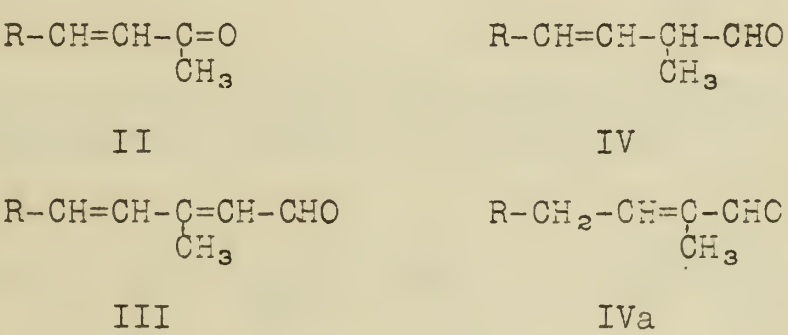
Karrer (9) established the generally accepted structure (I) for vitamin A in 1931. After confirming this work, Heilbron and coworkers (5) began a systematic study of polyene chemistry in an



I

attempt to synthesize the vitamin, and although they have never realized this goal, his group has helped immeasurably in laying the fundamental groundwork upon which later investigations have proceeded. While other attempts have been made to accomplish the synthesis (6) none appear to have been successful to the extent of yielding a biologically active substance until 1945. (The claim published by Kuhn and Morris (11) in 1937 has never been substantiated). Since that time syntheses of the acid (Ia) and alkyl ether (Ie) corresponding to vitamin A have been reported, and Milas (12) has patented methods for preparing the alcohol itself.

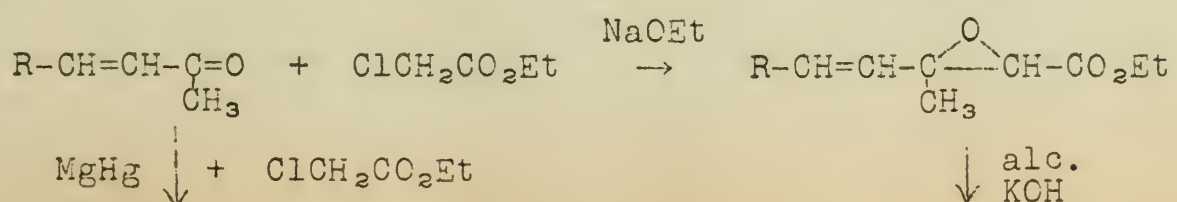
(1). Intermediates.--The starting point in all vitamin A syntheses has been β-ionone (II) (15) or some compound derived directly from it such as β-ionylidene acetaldehyde (III) or β-ionylidene formaldehyde (IV or IVa). (R = ring system in I).

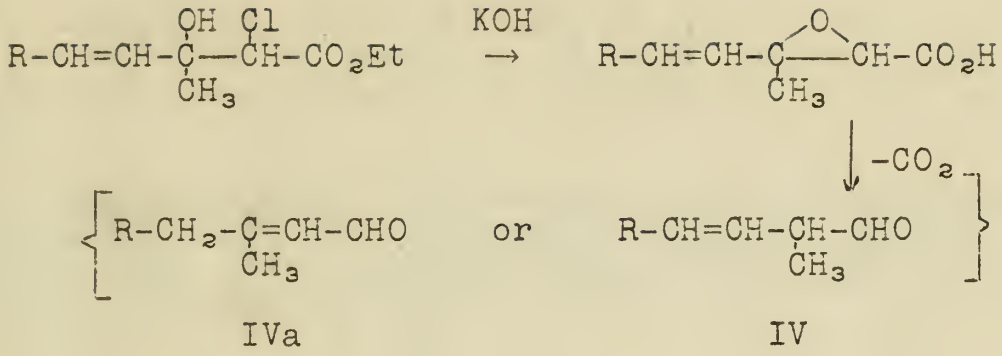


II IV

III IVa

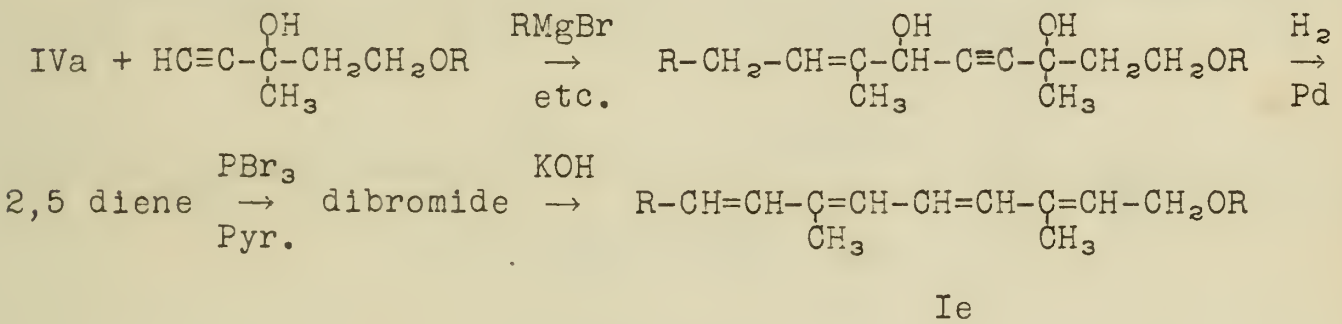
The failure to obtain III appears to have been the stumbling point in most of the earlier attempts (1,6). β-Ionylidene formaldehyde, used in several of the more recent syntheses may be prepared in the following manner: (5,12)



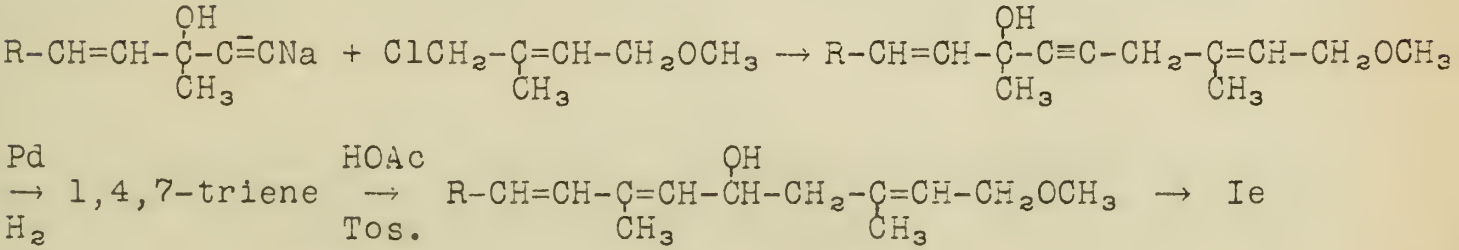


Heilbron (5) has shown by absorption spectra studies that IV is probably not formed in this reaction, and has assigned structure IVa to the product. Milas (12), however, assumes the structure to be represented by IV in all of his published schemes.

(2). Vitamin A Ether.--The methyl and ethyl ether of vitamin A have been prepared by Isler and coworkers (7), and Milas (12,13) by similar procedures.



Oroshnik (14) has varied this scheme somewhat by starting with the condensation product of β-ionone and acetylene.



Isler's methyl ether was reported to have the same absorption spectrum as vitamin A itself and on the basis of animal experiments appeared to be at least as active as β-carotene (i.e. about one half as active as vitamin A). Milas' methyl ether was approximately one thirty-fifth as active as pure vitamin A (13). Oroshnik (14) has not as yet reported on the activity of his product.

Pure crystalline vitamin A methyl ether prepared from the natural product has a potency of the same order of activity as crystalline vitamin A alcohol (i.e. 3,500,000 U.S.P. units per gram) (4).

(3). Vitamin A Acid.--Karrer and coworkers (8), and Van Dorp (16) have synthesized the acid corresponding to vitamin A utilizing in the first step the vinylog of bromoacetic ester in the Reformatsky condensation (2,3,18).

$$\text{II} + \text{BrCH}_2\text{CH=CHCO}_2\text{CH}_3 \xrightarrow{\text{Zn}} \rightarrow \text{R-CH=CH-C(CH}_3\text{)=CH-CH=CH-CO}_2\text{CH}_3$$

V

Unsaturated bromoesters of this type are prepared by means of N-bromosuccinimide (10,17).

Hydrolysis of the ester (V) gives the "C_{17} acid" which is converted to the higher acid by the following scheme.

$$\text{R-CH=CH-C(CH}_3\text{)=CH-CH=CH-CO}_2\text{H} \xrightarrow{PCl_3} \text{Acid Cl} \xrightarrow{CH_3ZnI} \text{R-CH=CH-C(CH}_3\text{)=CH-CH=CH-C(CH}_3\text{)=O}$$

$$\xrightarrow{CH_3Li,\ H_2O} \uparrow$$

$$\xrightarrow[\text{Zn}]{\text{BrCH}_2\text{CO-CH}_3}$$

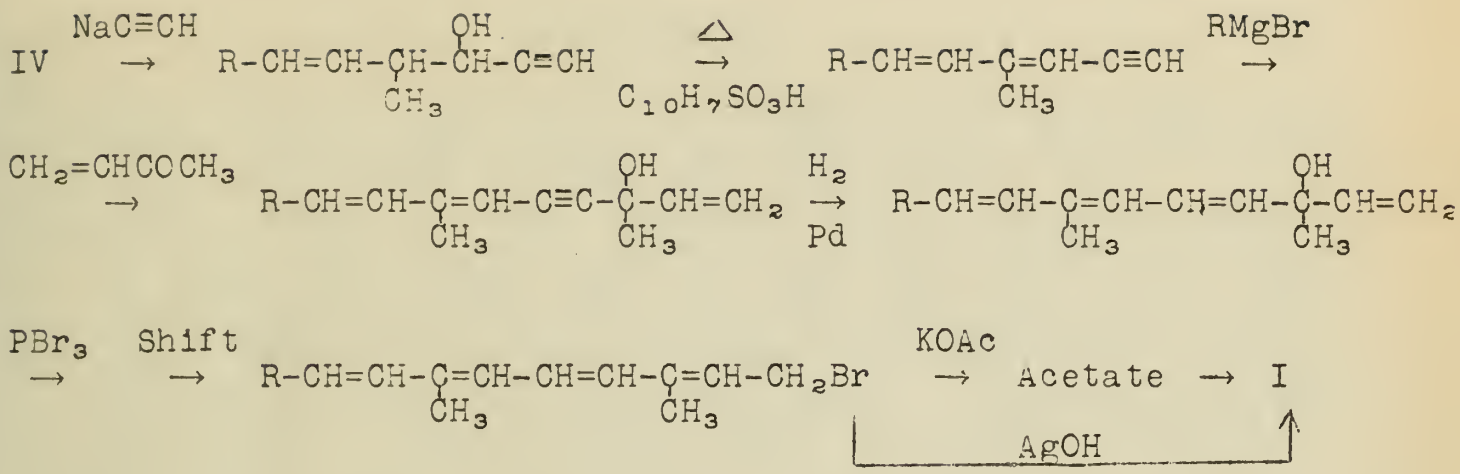
$$\rightarrow \text{R-CH=CH-C(CH}_3\text{)=CH-CH=CH-C(CH}_3\text{)=CH-CO}_2\text{CH}_3 \rightarrow \text{R-CH=CH-C(CH}_3\text{)=CH-CH=CH-C(CH}_3\text{)=CH-CO}_2\text{H}$$

Ia

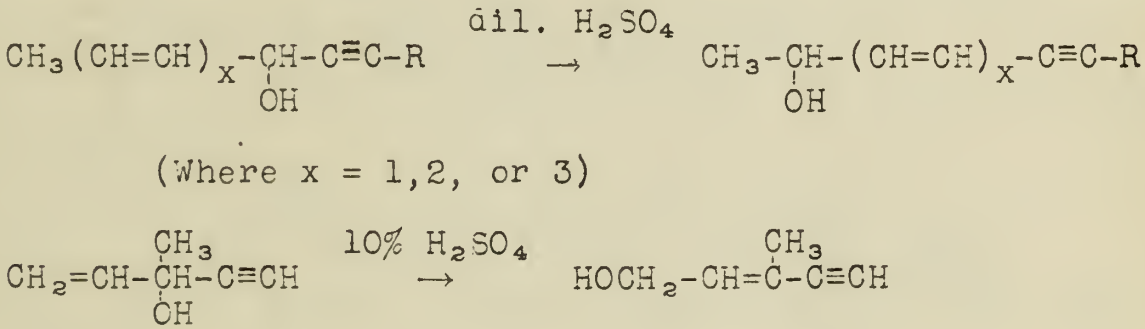
Heilbron's group (5-XXIV) succeeded in preparing the "C_{17} acid" and converted it to the "C_{18} ketone" by means of $Cd(CH_3)_2$, however, they have never reported a completion of the synthesis.

Van Dorp (16) indicated that his product was about one half as active as vitamin A. Karrer has not as yet reported any activity data.

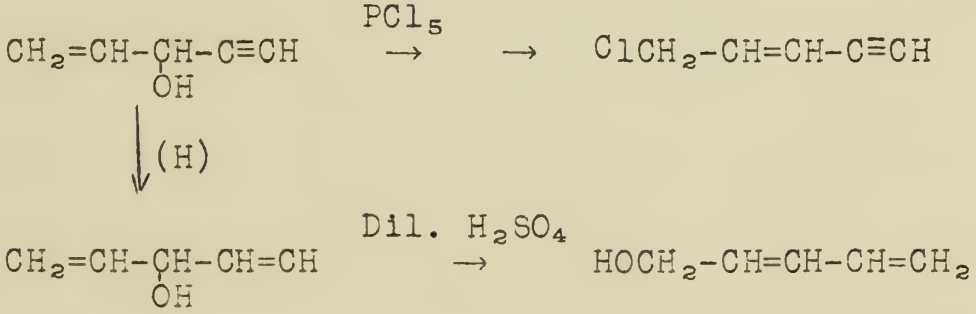
(4). Vitamin A Alcohol.--Milas (12) has patented several methods for the synthesis of the alcohol. The following is one of the more typical schemes.



Heilbron (5) has indicated that aniontropic rearrangements occur quite generally amongst α,β-unsaturated carbinols.



While vinyl ethynyl carbinol fails to undergo this shift even with 25% sulfuric acid, replacement of the -OH with Cl or Br leads to rearrangement. Semihydrogenation to the divinyl carbinol also facilitates the shift.



Milas has not specifically indicated the activity of his vitamin A alcohol but implies that it has about the same order of activity as the methyl ether which he prepared (i.e. 50,000 to 100,000 U.S.P. units per gram) (13).

Bibliography

(1) Boekelheide, Organic Seminar Abstracts, March 1, 1944.
(2) Fuson, Arnold and Cooke, J. Am. Chem. Soc., 60, 2272 (1938).
(3) Fuson and Southwick, ibid., 66, 679 (1944).
(4) Hanze, Conger, Wise and Weisblat, ibid., 68, 1389 (1946).
(5) Heilbron and coworkers, ("Studies in the Polyene Series"), J. Chem. Soc., 1939, 1549 (I); 1554 (II); 1557 (III); 1560 (IV); 1942, 727 (V); 733 (VI); 735 (VII); 1943, 261 (VIII); 264 (IX); 265 (X); 268 (XI); 1944, 134 (XII); 136 (XIII); 140 (XIV); 141 (XV); 144 (XVI); 1945, 77 (XVII); 81 (XVIII); 84 (XIX); 88 (XX); 90 (XXI); 1946, 27 (XXII); 500 (XXIII); 866 (XXIV). (Roman numerals refer to number in series).
(6) Heilbron, Jones and Bacharach, Vitamins and Hormones. II., 155 (1944).
(7) Isler, Kofler, Huber and Ronco, Experientia 2, 31 (1946); C.A., 40, 4032 (1946).
(8) Karrer, Jucker and Schick, Helv. Chim. Acta., 29, 704 (1946).
(9) Karrer, Morf and Schöpp, ibid., 14, 1036, 1431 (1931).
(10) Karrer and Schwyzer, ibid., 29, 1191 (1946).
(11) Kuhn and Morris, Ber., 70, 853 (1937).
(12) Milas, U.S. 2,369,156 to 2,369,167 (Feb. 13, 1945); C.A., 39, 5043-5046 (1945).
(13) Milas, Science, 103, 581 (1946).
(14) Oroshnik, J. Am. Chem. Soc., 67, 1627 (1945).
(15) Shotwell, Organic Seminar Abstracts, May 22, 1946.
(16) Van Dorp and Arens, Rec. Trav. Chim., 65, 338 (1946).
(17) Ziegler, Späth, Schaaf, Schumann and Winkelmann, Ann., 551, 80 (1942).
(18) Ziegler, Schumann and Winkelmann, ibid., 120.

Reported by Allen C. Moore
February 21, 1947

SYNTHESIS OF AMIDINES

I. Introduction.--Amidines have been prepared by a great many methods but until recently only three methods have had any considerable usage. None of these may be considered as a general preparative method for amidines, however, and for this reason the advent of a new, apparently general method is of considerable interest.

II. Preparation.--

1. From nitriles via the imino-ether (1):

$$RCN + ROH \xrightarrow{HCl} R\overset{\overset{NR}{\|}}{C}-OR\cdot HCl \xrightarrow{NH_3} R\overset{\overset{NH}{\|}}{C}-NH_2\cdot HCl$$

2. From amides via the amido-chloride (2):

$$R\overset{\overset{O}{\|}}{C}NHAr \xrightarrow{PCl_5} R-\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-NHAr \xrightarrow{ArNH_2} R-\overset{\overset{NAr}{\|}}{C}-NHAr$$

3. From nitrile and amine in the presence of sodium (3) (5):

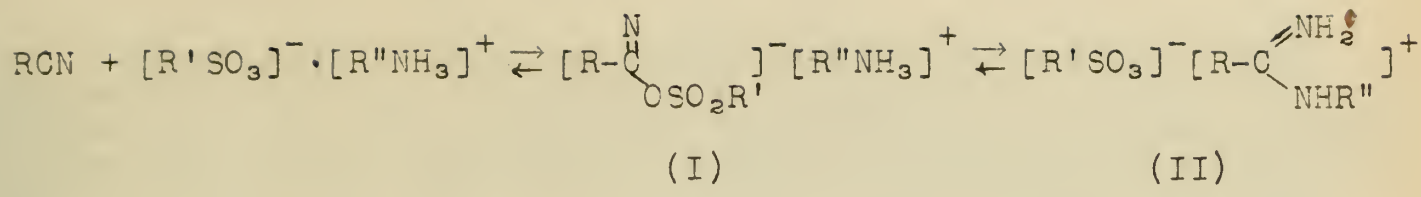
$$ArCN + ArNH_2 \xrightarrow{Na} Ar\overset{\overset{NNa}{\|}}{C}-NH-Ar \xrightarrow{H+} Ar-\overset{\overset{NH}{\|}}{C}-NHAr$$

4. From nitrile and ammonium- or amine-salt of a sulfonic acid (4) (New method):

$$\left.\begin{array}{l} R'SO_3NH_4 \\ \text{or} \\ R'SO_3H\cdot R''NH_2 \end{array}\right\} + RCN \xrightarrow{180\text{-}300^\circ} \left\{\begin{array}{l} R'SO_3H\cdot R\overset{\overset{NH}{\|}}{C}-NH_2 \\ \text{or} \\ R'SO_3H\cdot R-\overset{\overset{NH}{\|}}{C}-NHR'' \end{array}\right.$$

The last method mentioned above, although recently developed and as yet incompletely explored, appears to be general and may be used for the preparation of any amidine.

Oxley and Short (4) have proposed a mechanism for this reaction which involves the production of a complex anion (I) capable of degrading the ammonium ion to form the amidine salt of the sulfonic acid (II).



(I) (II)

III. Amidines as carbazylic acids.--Many of the reactions of amidines as well as their methods of preparation may be better understood by reference to the nitrogen system of compounds (5). In this system amidines are considered as acids (carbazylic by analogy with carboxylic in the oxygen system), and their reactions may be predicted on this basis.

Bibliography

1. Pinner, Ber., 10, 1889 (1877).
2. Hill, Rabinowitz, J. Am. Chem. Soc., 48, 732 (1926).
3. Walther, Grossmann, Jr. Pr. Chem., 78, 478 (1908).
4. Oxley, Short, J. Chem. Soc., 1946, 147.
5. Cornell, J. Am. Chem. Soc., 50, 3311 (1928).

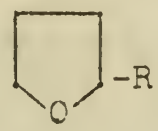
Reported by Norton A. Higgins
February 28, 1947

CLEAVAGE OF SOME CYCLIC ETHERS

Introduction.--With the recent availability of the tetrahydrofurans and the tetrahydropyrans, preparative methods utilizing these compounds have assumed new importance. Ring fission of such compounds provides convenient synthetic methods for obtaining aliphatic substances which are not readily accessible by any other routes.

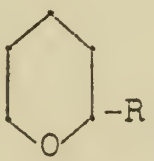
Cleavage with HX.--The usual ether cleavage with halogen acids is also applicable to the cyclic ethers. This reaction presents a most useful and desirable method for the preparation of 1,4- and 1,5-dihalides.

Oxidative cleavages.--Oxidative scissions do not often make useful preparative methods but they are helpful in locating ring substituents. Hydrogenated furans generally are split as follows.



$$+ \ KMnO_4 \rightarrow RCOOH + HOOC\text{-}COOH$$

However, tetrahydrofuran itself produces succinic acid. Tetrahydropyran is readily oxidized to glutaric acid, while the α-alkylated hydropyrans are oxidized as follows.

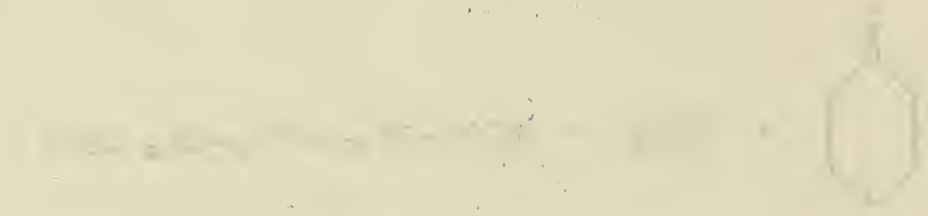


$$\xrightarrow{[O]} \quad RCOCH + HOOC\text{-}(CH_2)_2\text{-}COOH$$

If a tetrahydro-γ-pyrone structure is present or if the compound can be oxidized readily to such a structure the split occurs α to the carbonyl.

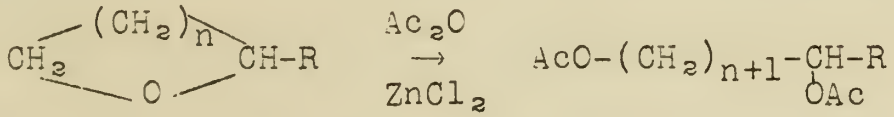
$$+ \ HNO_3 \rightarrow HOOC\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}COOH$$

Reductive cleavage.--Hydrofurans and hydropyrans both can be hydrogenated over PtO_2 under pressure with the formation of straight chain alcohols. Hydrogenation over Raney nickel usually



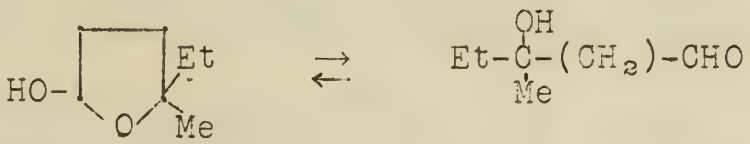
does not open the ring. If the hydrofuran ring has an α-alkyl substituent hydrogenative cleavage produces a primary alcohol.

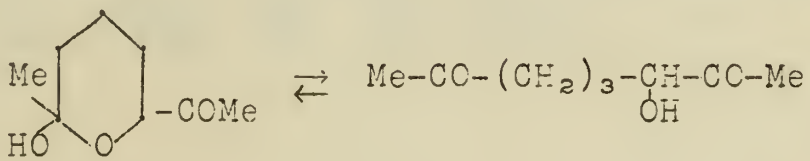
Cleavage with anhydrides or acid chlorides.--The ether linkage of these cyclic ethers is opened in the presence of acid anhydrides with the formation of glycol esters. The hydrogenated furans react much more readily than the hydrogenated pyrans.



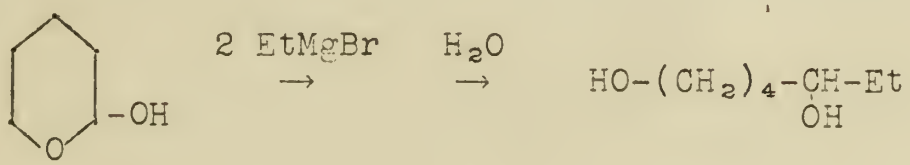
In many cases, especially with the pyrans, the acetate of the secondary hydroxyl loses acetic acid with the formation of the unsaturated derivative. If an acid chloride is substituted for the anhydride, chloroesters are produced.

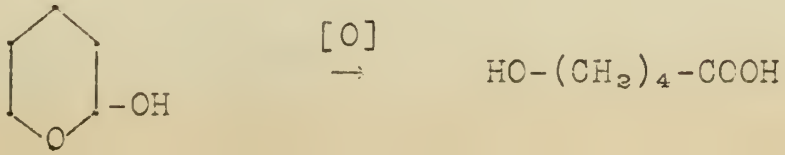
Straight chain-ring equilibria.--Hydrofurans and hydropyrans which contain a hydroxyl group in the α position are internal hemiacetals and have been shown to exist in equilibrium with the straight chain aldehyde or ketone.

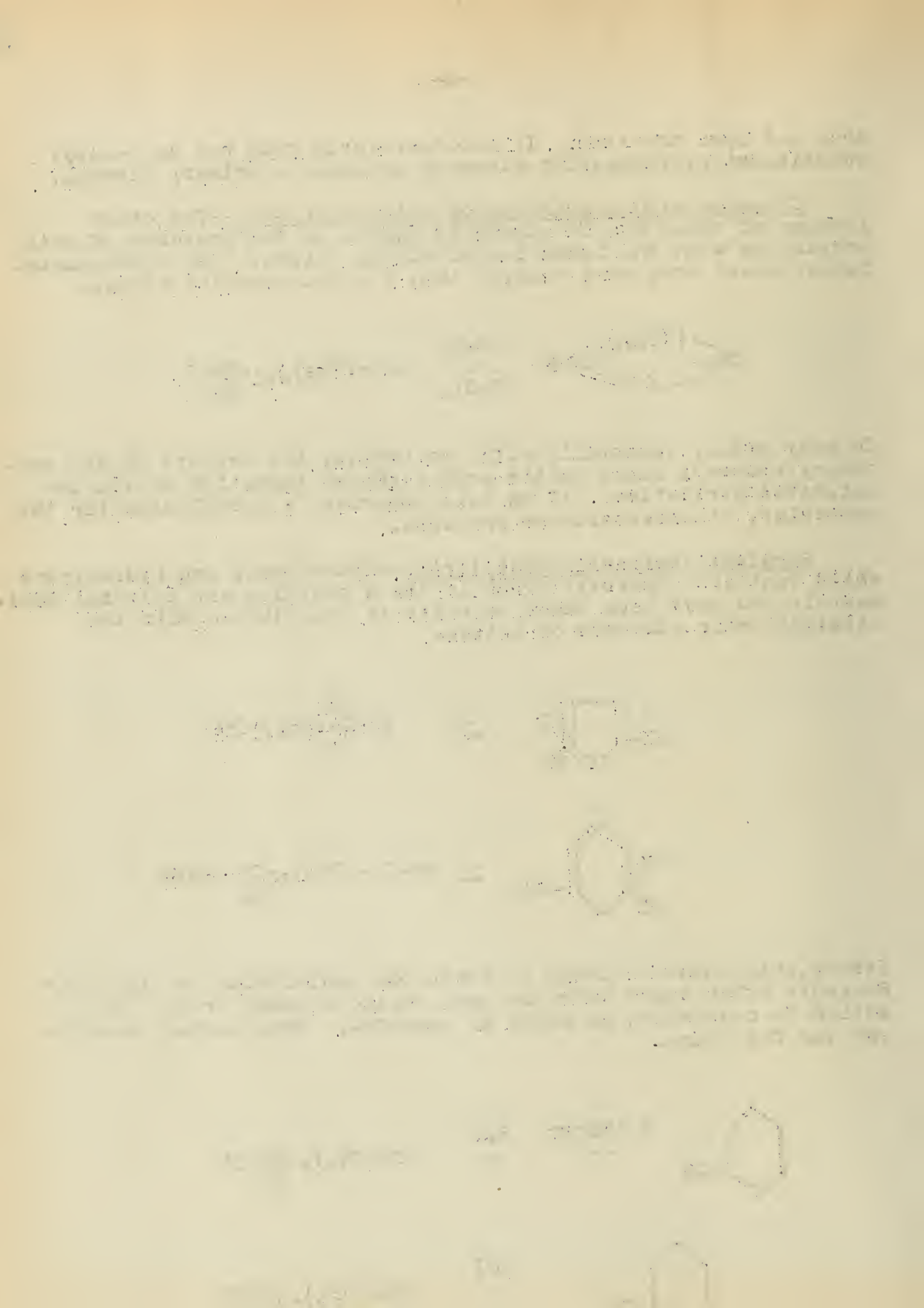


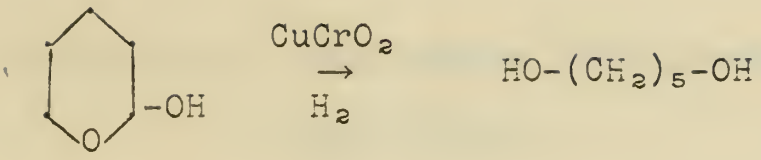


Strong acid solution tends to force the equilibrium to the right. Reagents which react with the open chain compound drive the reaction to completion as would be expected. Some useful examples are the following.









These are good preparative methods for the diols and γ and δ hydroxy acids.

Bibliography

1. Paul, Compt. rend., 218, 122 (1944); 212, 398 (1941); 208, 587 (1939); 198, 375, 1246 (1934); 197, 1652 (1933); 196, 1409 (1933); 195, 1289 (1932).
2. Paul, Bull. soc. chim., 8, 369 (1941); 6, 1162 (1939); 5, 919, 1053 (1938); 2, 311, 745 (1935); 1, 971, 1397 (1934); 53, 417, 1489 (1933).
3. Fuson, Christ and Bradsher, J. Org. Chem., 4, 401 (1939).
4. Wilson, Nature, 157, 846 (1946); J. Chem. Soc., 1945, 48.
5. Helferich, Ber., 52B, 1123 (1919).
6. Helferich and Malkomes, ibid., 55B, 702 (1922).
7. Takamoto, Chem. Abs., 21, 3362 (1927); 22, 3162 (1928); 23, 387 (1929).
8. Baker, J. Chem. Soc., 1944, 296.
9. Franke and Lieben, Monatsche., 43, 225 (1922).
10. Schniepp and Geller, J. Am. Chem. Soc., 68, 1646 (1946).
11. Fried and Kleene, ibid., 62, 3258 (1940).
12. Cloke and Pilgrim, ibid., 61, 2667 (1939).

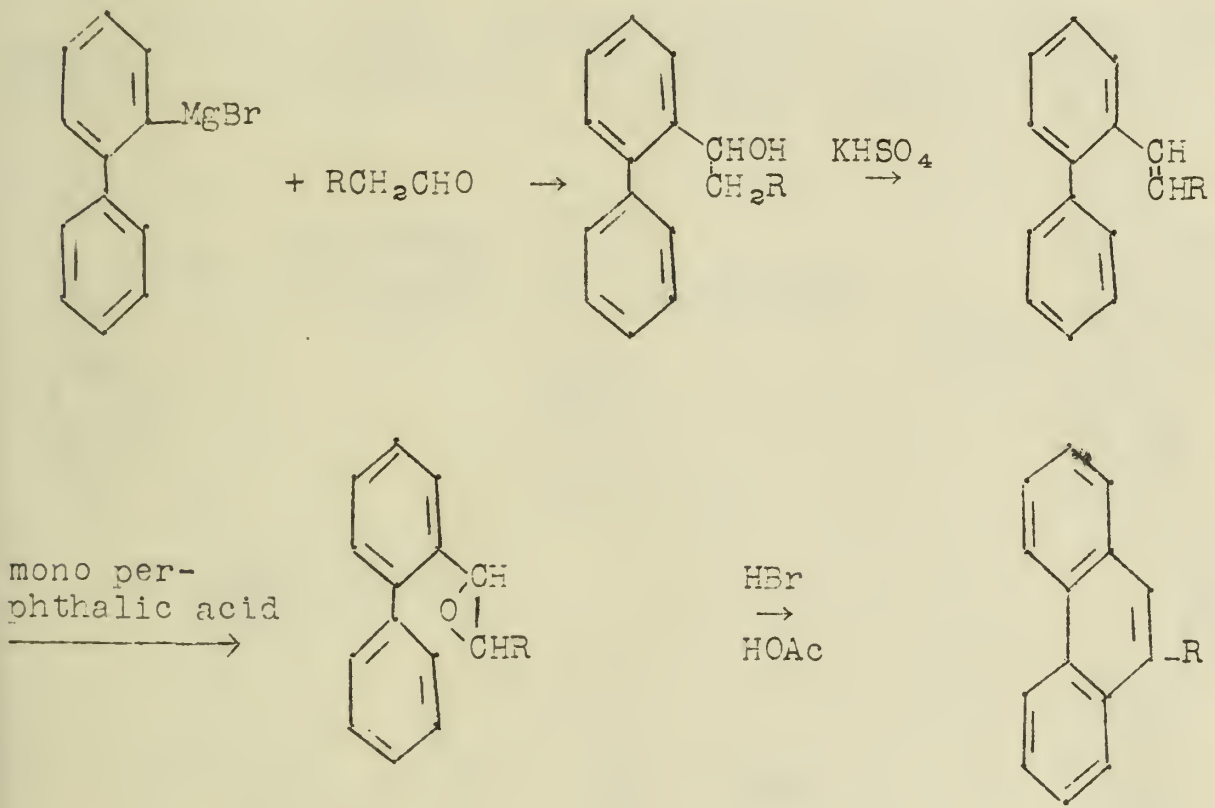
Reported by Elliot N. Marvell
February 28, 1947

SYNTHESIS OF PHENANTHRENE DERIVATIVES

BY CYCLIZATION

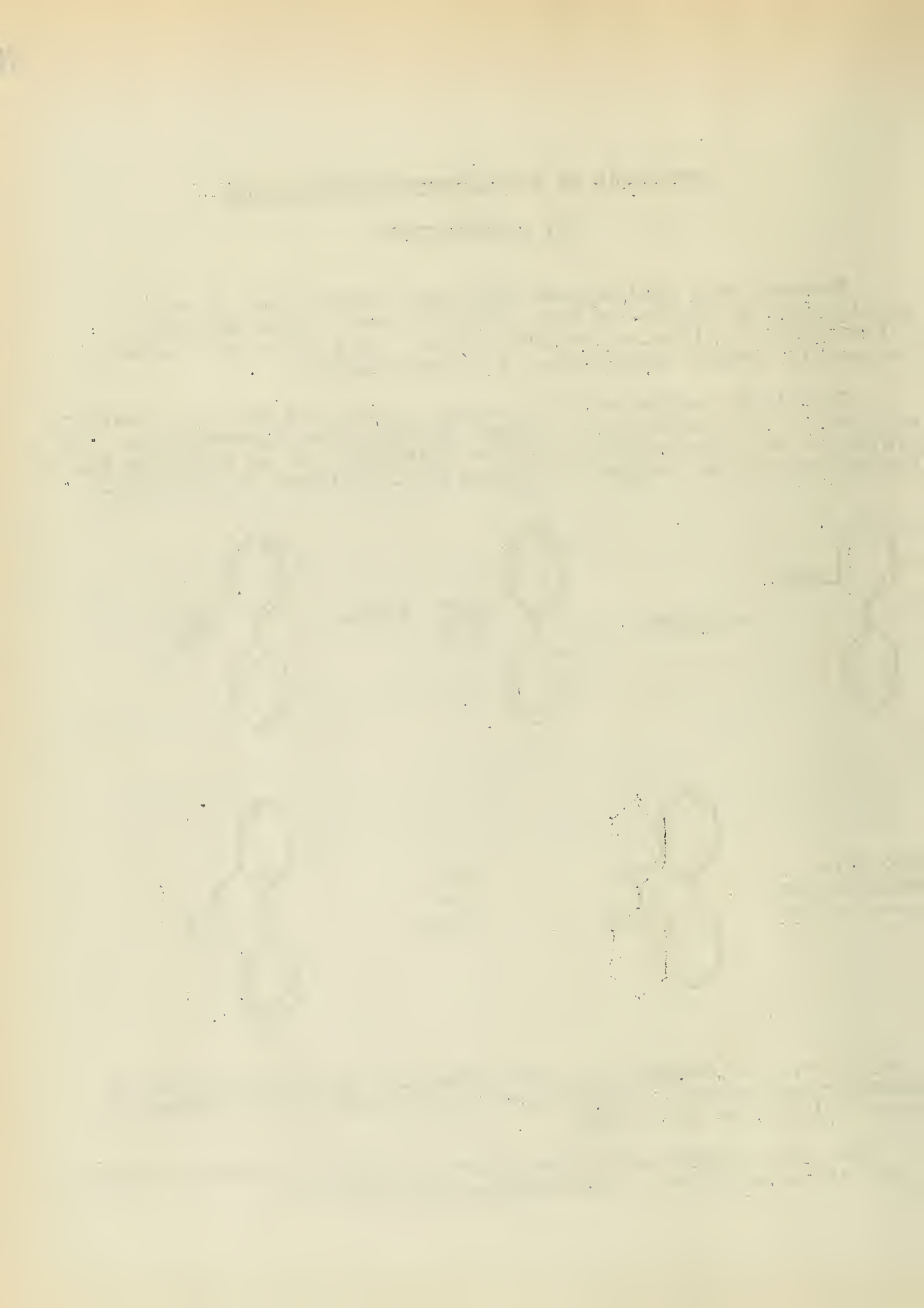
Phenanthrene derivatives have been synthesized by the cyclization of olefin oxides, glycol ethers, amino alcohols, chlorohydrins, glycols, ketones, acids, acid chlorides, amines, oxalacetic esters, dibromides, and hydrocarbons.

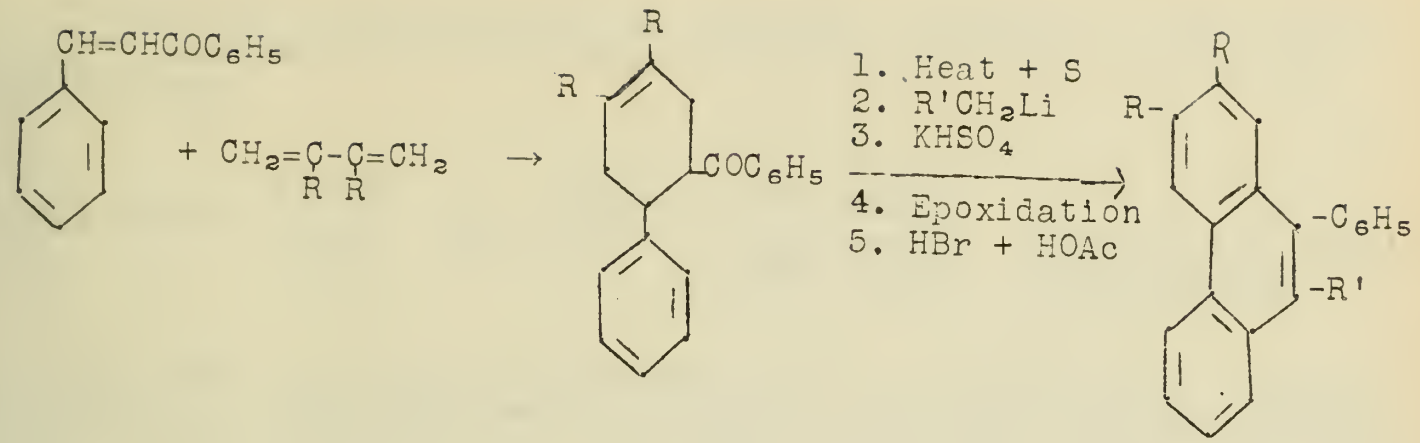
The olefin oxide method of ring closure has been successfully applied to the preparation of many phenanthrene derivatives. The synthesis of a 9-alkylphenanthrene starting with an aldehyde and 2-biphenylmagnesium iodide will serve to illustrate this method.



In addition to aldehydes the above reaction has been applied to unsymmetrical ketones, symmetrical ketones and cyclic ketones in overall yields of 20 to 40%.

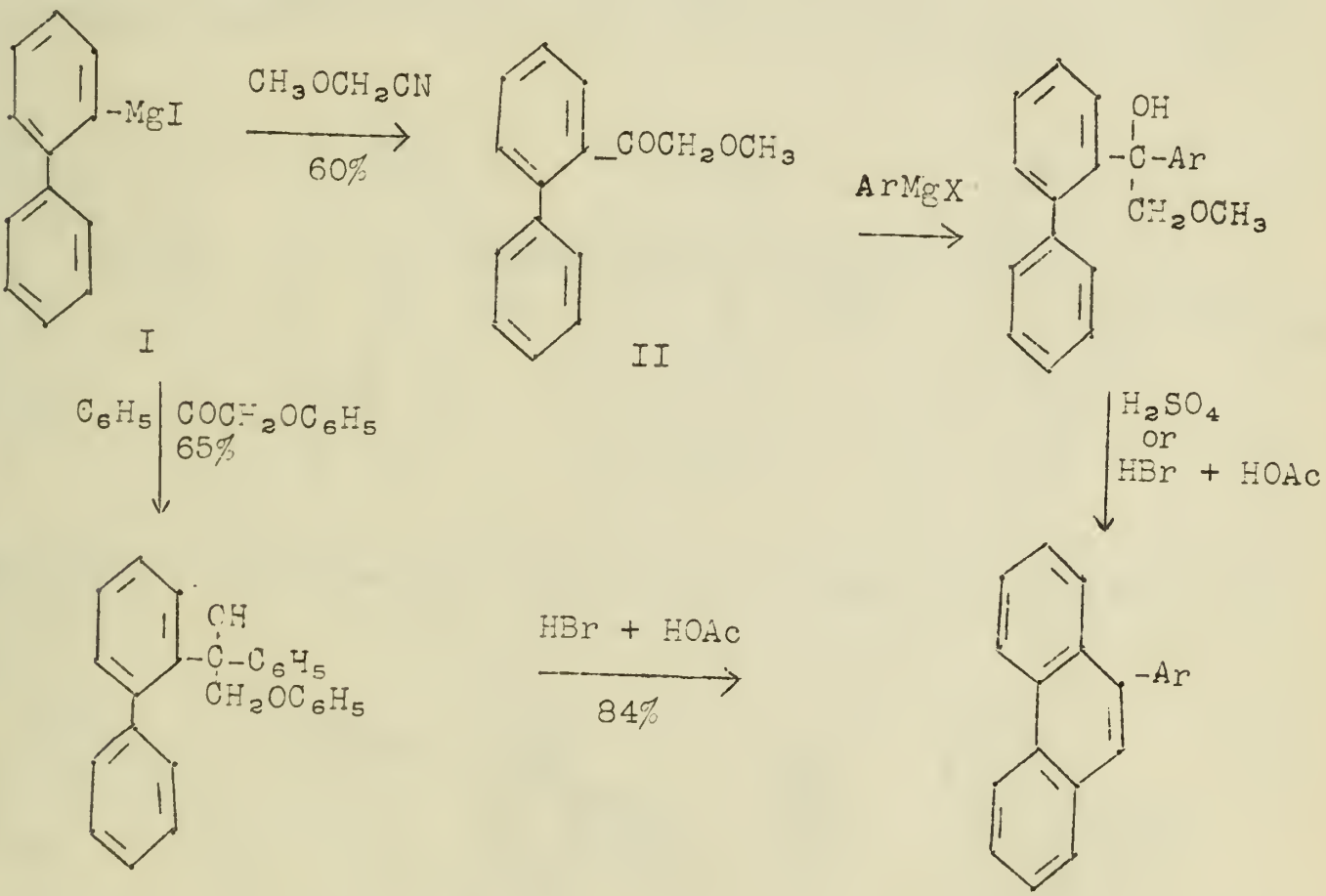
The olefin oxide method has been applied to products obtained by the diene addition to α,β-unsaturated ketones.





Efforts were made to block the aromatization of the olefin oxide by substituting it completely, but a molecule of alcohol was eliminated in place of water and aromatization occurred.

The glycol ether (β-methoxy carbinol or β-phenoxy carbinol) method of ring closure has been applied rather generally to the synthesis of phenanthrene derivatives. 9-Ethyl-, 9-n-propyl-,



9-n-butyl-, and 9-benzylphenanthrene were prepared in yields of 54, 51, 40, and 70% respectively. In an attempt to prepare 9-isopropyl-phenanthrene only phenanthrene was isolated.

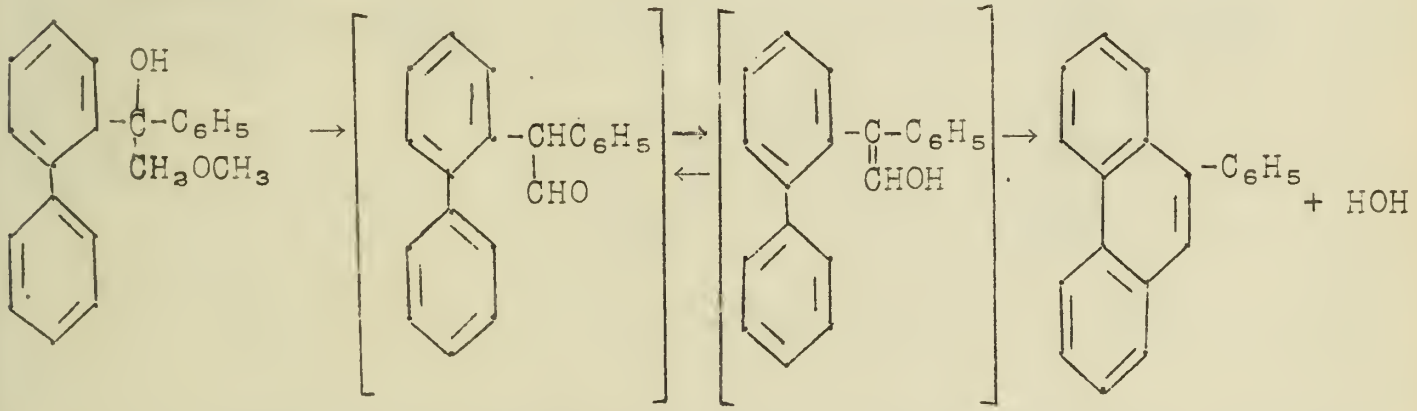
Similarly, 9, 10-diphenyl-, 9-methyl, 10-phenyl-, and 9-ethyl, 10-phenylphenanthrene were obtained in yields of 62, 72, and 35% respectively.

$$C_6H_5COCHX\text{-}R \xrightarrow[K_2CO_3]{C_6H_5OH} C_6H_5COCH(OC_6H_5)\text{-}R \xrightarrow[2.\ HBr + HOAc]{1.\ O\text{-}C_{12}H_9MgI} \text{9,10-disubstituted Phenanthrene}$$

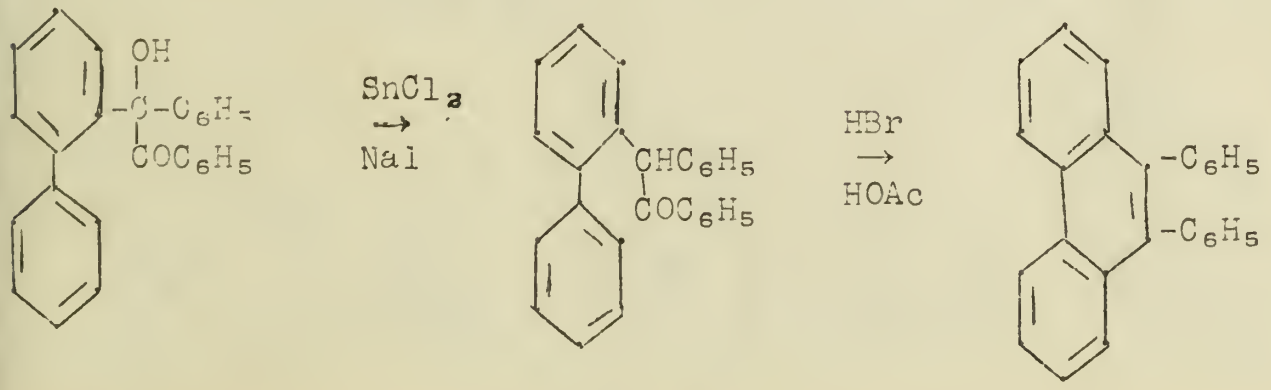
In order to obtain phenanthrene with no substituents in the 9, 10 position, 2-(ω-methoxyaceto)-biphenyl (compound II) was reduced with aluminun isopropylate to the methoxy carbinol which in turn was cyclized to phenanthrene in an overall yield of 46%.

In the synthesis of 9-methylphenanthrene β-methoxy carbinols, and β-phenoxy carbinols gave overall yields of 30 to 32%, while chlorohydrins and amino alcohols gave overall yields of only 1 to 10%. β-Phenoxy carbinols were cyclized by the Friedel and Crafts reaction in 10% yields.

The following mechanism has been proposed for the cyclization of methoxy carbinols. As proof of the proposed mechanism the



cyclization of ketones and isolation of ketone intermediates were attempted.



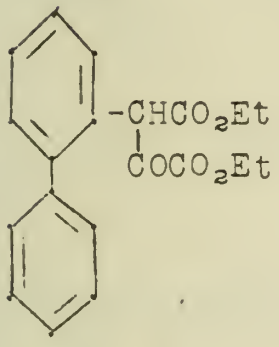
Compound V was also isolated from the conventional β-phenoxy carbinol reaction and identified.

Glycols were also cyclized. Treatment of benzoin with 2 moles of 2-biphenyl magnesium iodide gave a glycol which was cyclized to 9,10-diphenylphenanthrene in an overall yield of 29% (calculated from benzoin).

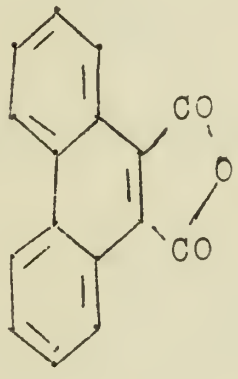
Another synthesis of phenanthrene derivatives involves the cyclization of oxalacetic ester derivative as shown below.

R = ()

RCO_2H —(1. oxalyl chloride, 2. CH_2N_2)→ $RCOCHN_2$ —(aquerous colloidal Ag)→ RCH_2CO_2H —(ethyloxatate on the ester)→

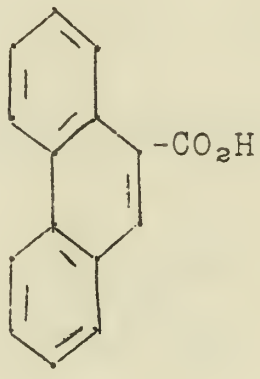


HBr → HOAc



13%

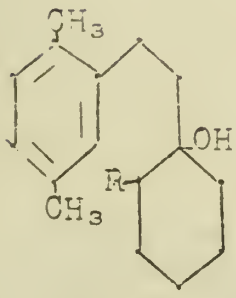
+



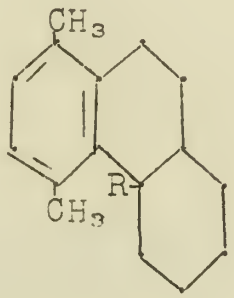
67%

1,4,Dimethylphenanthrene has been prepared by three methods:

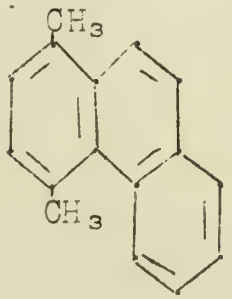
(1) Cyclization by means of phosphorus pentoxide.
R = H or CH_3

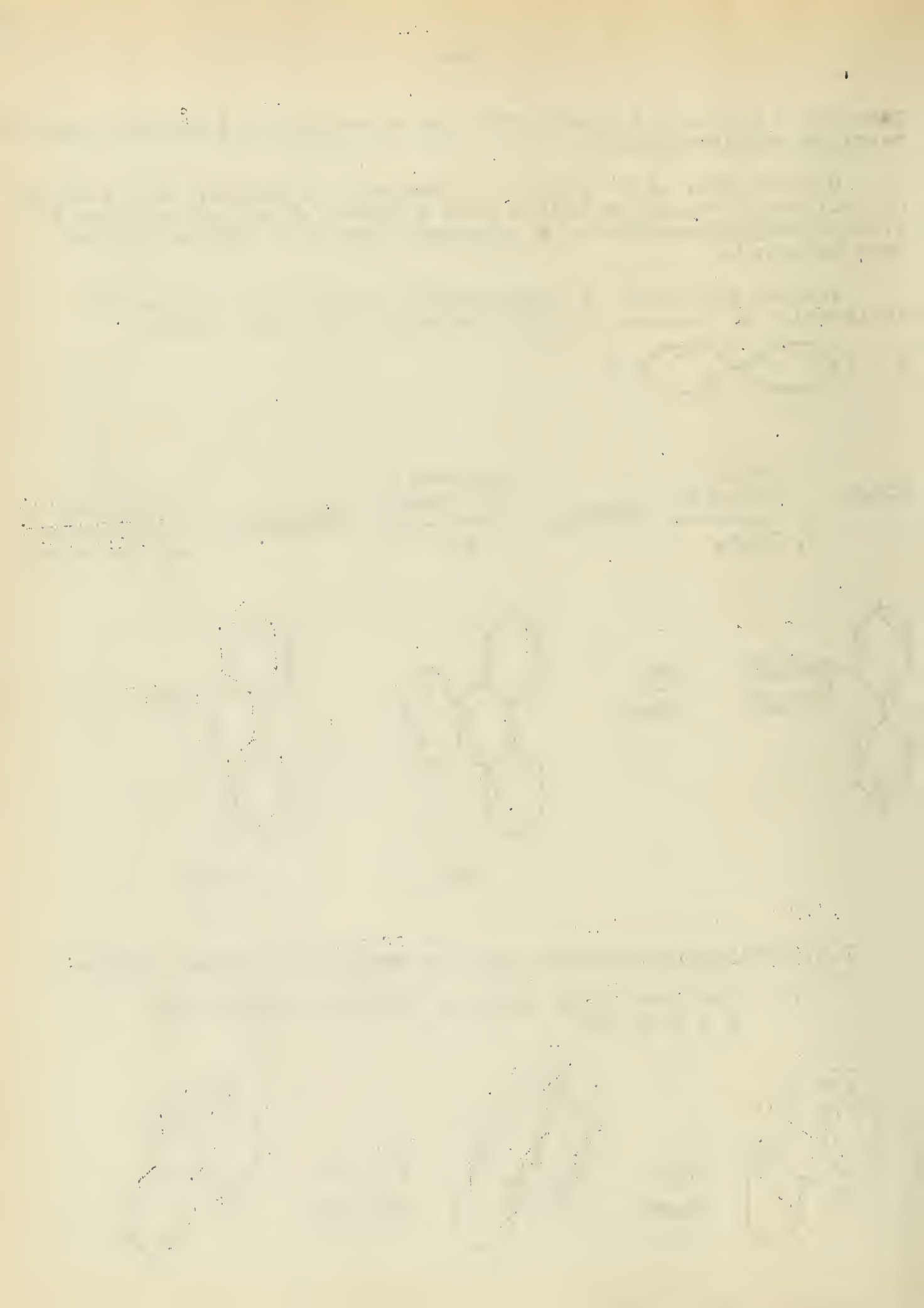


P_2O_5 → 82-86%

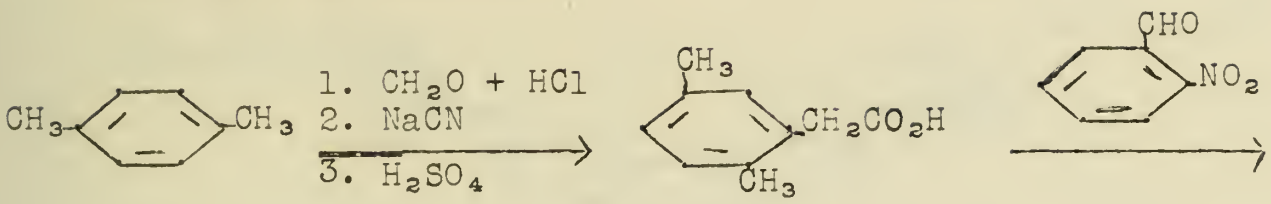


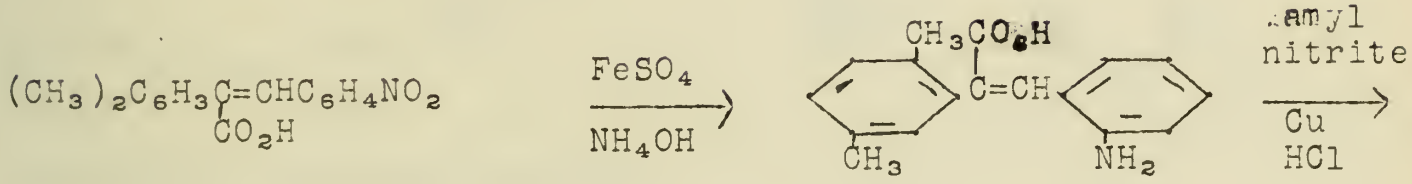
S or Se → 340-350°

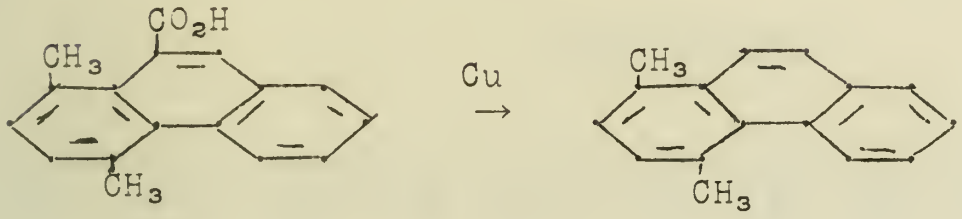




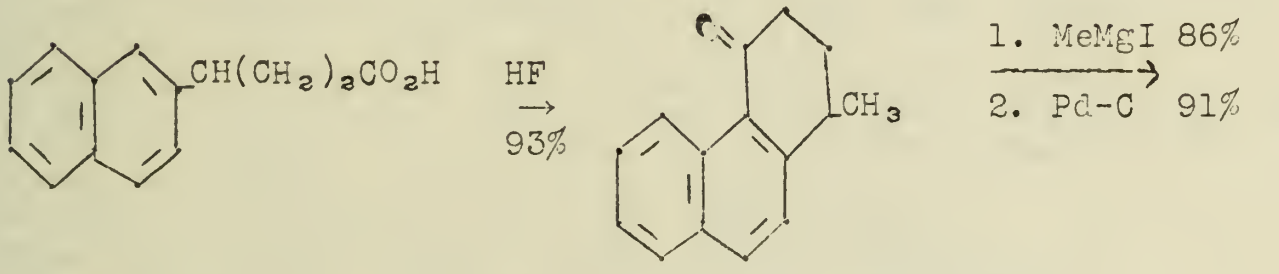
(2) Pschorr Reaction

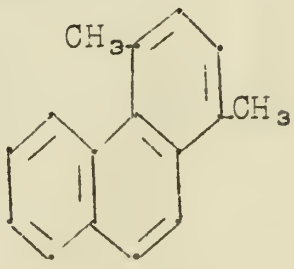






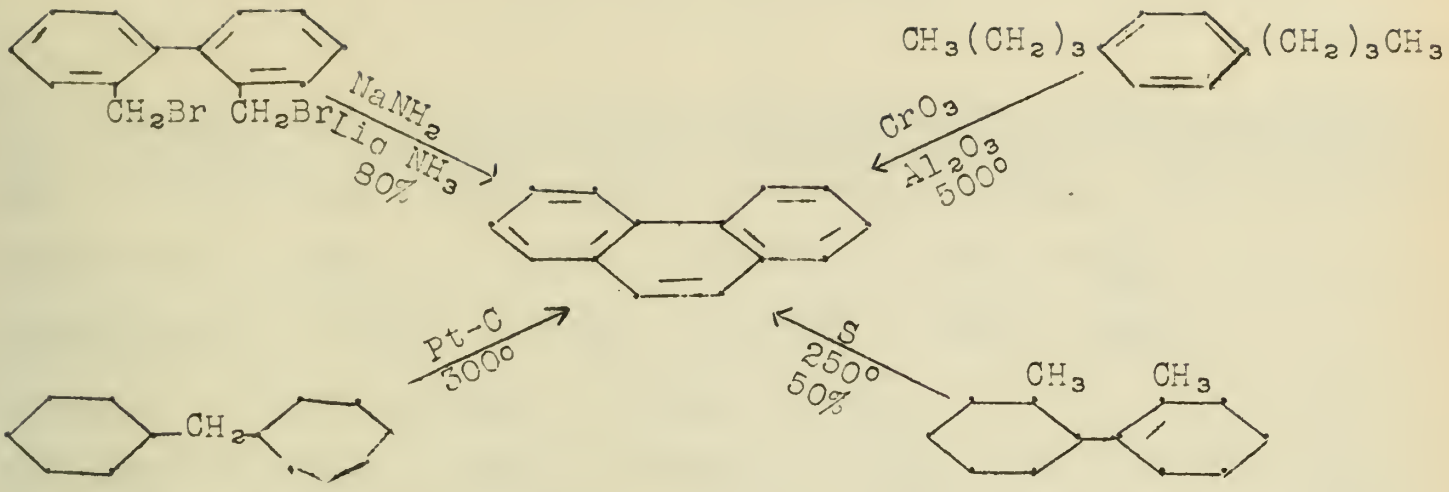
(3) Cyclization of an acid by use of anhydrous hydrogen fluoride.





A mixture of zinc chloride and acetic anhydride has been used for cyclization of acids in yields of 90%. Aluminum chloride has been used for the cyclization of acid chlorides in good yields.

Phenanthren has been prepared by the following methods.



cyclohexyl cycloheptyl methane

BIBLIOGRAPHY

Bradsher and Co-workers J. Am. Chem. Soc.; 60, 2960 (1938); 61, 1524, 2184, 3131, (1939); 62, 2306 (1940); 63, 493 (1941); 65, 1646, 2016, 2304 (1943); 66, 1280, 1281, (1944); 68, 1094, 2152, 2149 (1946).
Geissman and Tess, J. Am. Chem. Soc., 62, 514 (1940).
Schonberg and Warren, J. Chem. Soc., 1938 (1939).
Karasch, Nudenberg, and Fields, J. Am. Chem. Soc., 66, 1276 (1944).
Wilds and Beck, ibid., 66, 1688 (1944).
Johnson, Goldman and Schneider, ibid., 67, 1357 (1945).
Mattox and Grosse, ibid., 67, 84 (1945).
Elagina and Zelinskii, Chem. Abstracts, 37, 616 (1943).
Elagina and Zelinskii, Compt. rend. acad. sci., U.S.S.R. 30, 728 (1941)
Orcutt and Bogert, J. Am. Chem. Soc., 63, 127 (1941).
Fieser and Daudt, ibid., 63, 782 (1941).
Beckmann and Sheehan, ibid., 63, 2598 (1941).
Papa, Perlman and Bogert, ibid., 60, 319 (1938).
Akins, Stamatoff and Bogert, ibid., 59, 1268 (1937).

Reported by Rupert E. Light, Jr.

March 7, 1947

PERIODATE OXIDATIONS

Periodic acid oxidation has been considered a specific reaction for 1,2-glycols, α-aminoalcohols, α-hydroxyaldehydes, α-hydroxyketones, and 1,2-diketones; α-hydroxyacids are slowly oxidized, if at all (1).

$RCHOHCHOHR' + HIO_4 \rightarrow RCHO + R'CHO + HIO_3 + H_2O$

$RCHOHCHNH_2R' + HIO_4 \rightarrow RCHO + R'CHO + HIO_3 + NH_3$

$RCHOHCHO + HIO_4 \rightarrow RCHO + HCO_2H + HIO_3$

$RCHOHCOR' + HIO_4 \rightarrow RCHO + R'CO_2H + HIO_3$

$RCOCOR' + HIO_4 + H_2O \rightarrow RCO_2H + R'CO_2H + HIO_3$

$RCHOHCO_2H + HIO_4 \rightarrow RCHO + CO_2 + HIO_3 + H_2O$

However recently it has been shown that certain α-ketoacids (2,3), active methylene compounds (2,3), enediols (2,3), phenols (4), and aromatic amines (4) are readily oxidized by periodate in aqueous solution at room temperature using one to two times the theoretical amount of oxidant required for complete oxidation.

Oxidation of α-ketoacids (2,3).

Only three α-ketoacids, glyoxylic acid, mesoxalic acid, and oxalacetic acid, are readily oxidized by periodate. Pyruvic acid,

$OHCCO_2H + HIO_4 \rightarrow HCO_2H + CO_2 + HIO_3$

$HO_2CCOCO_2H + HIO_4 \rightarrow HO_2CCO_2H + CO_2 + HIO_3$

$HO_2CCOCH_2CO_2H + HIO_4 \rightarrow CO_2 + HIO_3 + HO_2CCH_2CO_2H \xrightarrow{HIO_4\ \text{further}}$ oxidation

α-ketobutyric acid, and α-ketoglutaric acid are oxidized very slowly.

β-Hydroxy-α-ketoacids such as hydroxypyruvic acid, β-hydroxy-α-ketobutyric acid, and 2-keto-d(l)-gluconic acid are oxidized, but the α-ketoacid structure is destroyed by the preferential oxidation as an α-hydroxyketone.

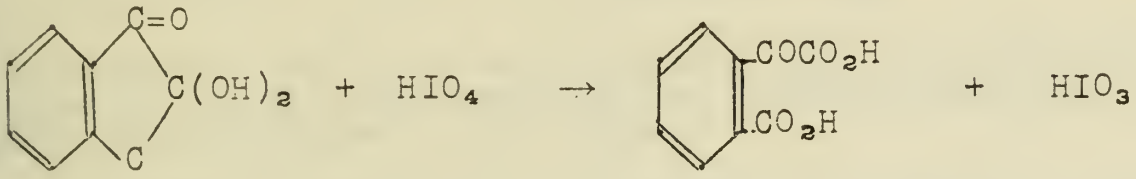
$HOCH_2COCO_2H + HIO_4 \rightarrow HCHO + HO_2CCO_2H + HIO_3$

Compounds of other types which would be expected to give α-ketoacids during periodate oxidation have been investigated. It is feasible to write either glyoxylic acid or mesoxalic acid as an intermediate for the following compounds: mucic acid, d-saccharic acid, dl-serine, dl-threonine, glyceric acid, tartaric acid, d-gluconic acid, 5-keto-d-gluconic acid, d-glucuronic acid, d-fructose, l-sorbose, meso-inosose, dipotassium rhodizonate, and dipotassium croconate.

$HO_2C(CHOH)_4CO_2H + 3HIO_4 \rightarrow 2HO_2CCHO + 2HCO_2H + H_2O + 3HIO_3$

$HO_2CCHO + HIO_4 \rightarrow HCO_2H + HIO_3$

The oxidation of triketohydrindene hydrate is particularly interesting since it indicates that β-phenyl-α-ketoacids are not oxidized.



The importance of experimental conditions is demonstrated by the oxidation of tartaric acid. In dilute, weakly alkaline solution

$HO_2C(CHOH)_2CO_2H + HIO_4 \rightarrow 2HO_2CCHO + HIO_3 + H_2O$

$2HO_2CCHO + 2HIO_4 \rightarrow 2CO_2 + 2HCO_2H + 2HIO_3$

containing a moderate excess of periodic acid, tartaric acid consumed almost 3 moles of periodate and liberated 2 moles of carbon dioxide at room temperature in 20-30 minutes. Even with less than the theoretical amount of oxidant rapid oxidation occurred. In dilute acid solution intermediate effects were noted, and in strong acid solution or at 5°C. the secondary oxidation was considerably reduced.

Oxidation of certain active methylene compounds (2,3).

The active methylene group of certain β-carbonyl compounds is oxidized by periodate to a hydroxyl group. Subsequent oxidation

$CH_3COCH_2CO_2H + HIO_4 \rightarrow CH_3COCHOHCO_2H + HIO_3$

$CH_3COCHOHCO_2H + 2HIO_4 \rightarrow CH_3CO_2H + HCO_2H + CO_2 + 2HIO_3$

follows conventional routes.

The configuration necessary for this type of oxidation is a three carbon system consisting of a free carboxyl or aldehyde group, an α-carbon bearing at least one hydrogen atom, and a β-carbonyl which may be part of an aldehyde, ketone, carboxyl, carbalkoxyl, or similar activating group.

Malonic acid has been extensively investigated. The primary oxidation product is tartronic acid. This is oxidized further,

$HO_2CCH_2CO_2H + HIO_4 \rightarrow HO_2CCHOHCO_2H + HIO_3$

mainly to formic acid and carbon dioxide, but a small amount is

$HO_2CCHOHCO_2H + HIO_4 \rightarrow OHCCO_2H + CO_2 + HIO_3$

$OHCCO_2H + HIO_4 \rightarrow HCO_2H + CO_2 + HIO_3$

oxidized by either iodate or periodate to mesoxalic acid, which yields carbon dioxide and oxalic acid. Monoethylmalonate, and

$$HO_2CCHOHCO_2H + HIO_4 \rightarrow HO_2CCOCO_2H + H_2O + HIO_3$$

$$HO_2CCOCO_2H + HIO_4 \rightarrow HO_2CCO_2H + CO_2$$

α-ethylmalonic acid also are oxidized, but diethylmalonate, cyanoacetic acid, ethylcyanoacetate, ethylacetoacetate, acetylacetone, and ethyloxomalonate do not react.

A number of compounds which would be expected to yield an active methylene compound with the necessary configuration during periodate oxidation were also investigated. In each of the following compounds it is plausible to write an active methylene compound as an intermediate: malic acid, digitoxose, oxalacetic acid, citric acid, 1,4-anhydrosorbitol, 5-keto-d-gluconic acid, and d-glucuronic acid.

$$HO_2CCHOHCH_2CO_2H + HIO_4 \rightarrow OHCCH_2CO_2H + CO_2 + H_2O + HIO_3$$

$$OHCCH_2CO_2H + HIO_4 \rightarrow OHCCHOHCO_2H + HIO_3$$

$$OHCCHOHCO_2H + 2HIO_4 \rightarrow 2HCO_2H + CO_2 + 2HIO_3$$

Oxidation of enediols (2,3).

Apparently periodate oxidizes enediols to α-diketones. Further oxidation proceeds as usual for α-diketones. Dihydroxymaleic acid, dipotassium rhodizonate, and dipotassium croconate are compounds which undergo this type of oxidation.

$$HO_2CCOH=COHCO_2H + HIO_4 \rightarrow HO_2CCOCOCO_2H + H_2O + HIO_3$$

$$HO_2CCOCOCO_2H + HIO_4 + H_2O \rightarrow 2HO_2CCO_2H + HIO_3$$

Oxidation of phenols and aromatic amines (4).

Certain phenols and aromatic amines with a critical oxidation potential of 1.04 or less are oxidized by periodic acid. These are resocinol, p-cresol, β-naphthol, 5-chlorovanillic acid, guaiacol, vanillic acid, vanillyl alcohol, cresol, phloroglucinol, α-naphthol, ferulic acid, catechol, hydroquinone, p-aminocinnamic acid, and p-anisidine. Acetylvanillic acid does not react. Phenol and vanillin have a critical oxidation potential larger than 1.04 and also do not react.

There is no direct relationship between the magnitude of the critical oxidation potential and the rapidity and extent of oxidation. For example phloroglucinol which has a critical oxidation potential of 0.799 volts consumes 0.5 mole of periodate slowly, while guaiacol at 0.868 volts consumes 3 moles rapidly. Evidently a phenolic hydroxyl group must be unsubstituted since vanillic acid is oxidized but acetylvanillic acid is not.

The nature of the oxidation is not known. Attempts to isolate definite products from the oxidation of vanillic acid and ferulic acid were unsuccessful. However since many of the compounds consumed 3 or more moles of the oxidant it is assumed that the aromatic nucleus is attacked.

BIBLIOGRAPHY

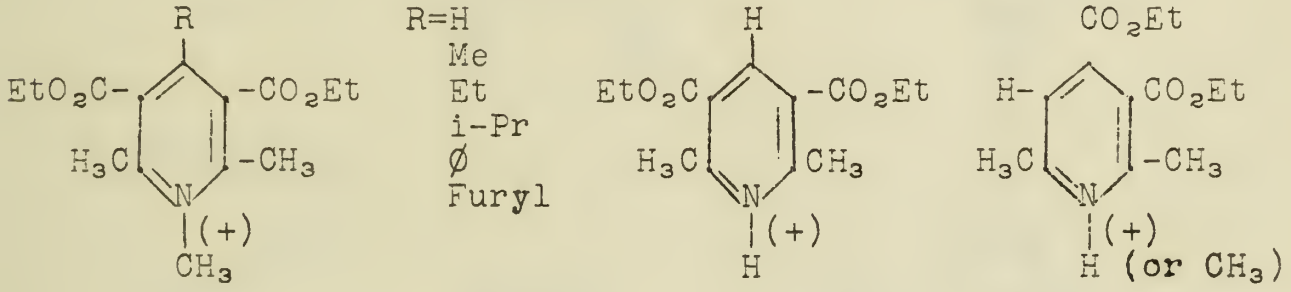
(1) Jackson in Adams, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 341.
(2) Sprinson and Chargaff, J. Biol. Chem., 164, 433 (1946).
(3) Huebner, Ames, and Bubl, J. Am. Chem. Soc., 68, 1621 (1946).
(4) Pennington and Ritter, J. Am. Chem. Soc., 69, 187 (1947).

Reported by J. H. Koehneke
March 7, 1947

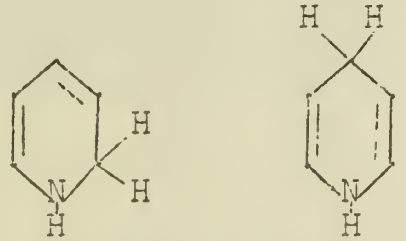
REVERSIBLE REDUCTION OF PYRIDINES

I. Introduction.--When quaternary pyridinium derivatives are partially reduced, a yellow bimolecular reduction product is formed, then the dihydropyridines. This reversible reduction has been identified with one step in the oxidation reduction processes in the human body. The bimolecular reduction product has recently been used in the synthesis of 4-alkylated pyridines.

Some simpler derivatives of pyridine were studied, and an analogy shown between their behavior and that of the codehydrogenase molecules known to contain a nicotinamide molecule in a quaternary pyridinium union with a ribose residue. The compounds studied were:



II. Experimental.--A study was made of the preparation and properties of the dihydropyridines. In the reduction, the quaternary nitrogen was changed to a tertiary nitrogen, fixing the place of entry of one hydrogen atom at the nitrogen. In only two dihydropyridines is this possible. They are:



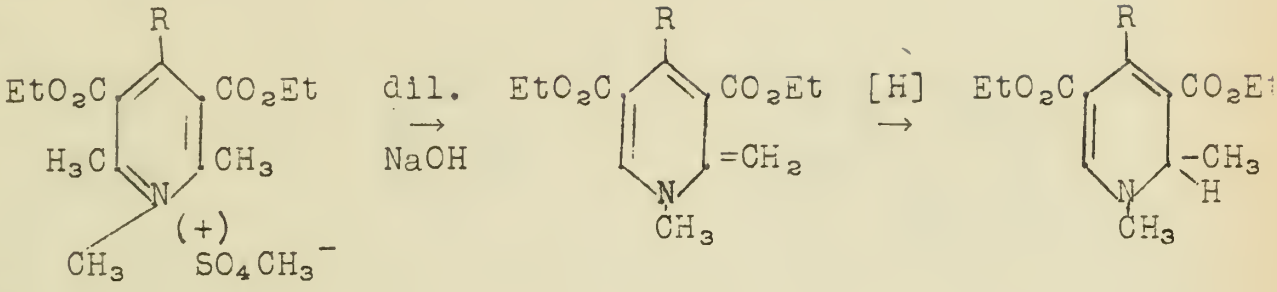
α-dihydro γ-dihydro

It is then necessary to determine the place of entry of the second hydrogen atom.

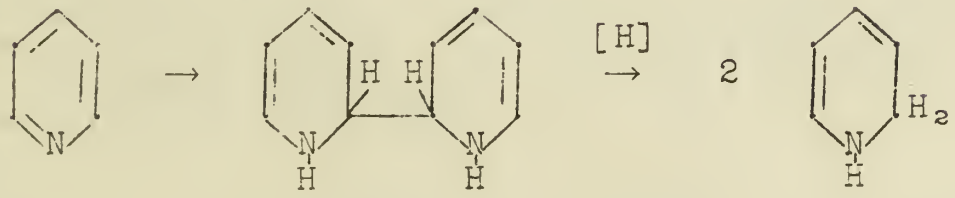
Preparation of dihydropyridines:

A. α-dihydro

1.

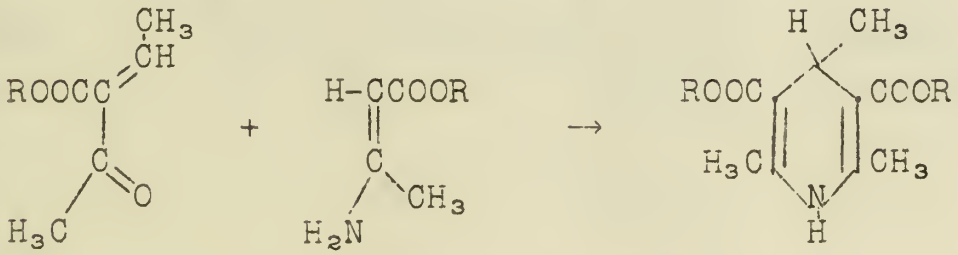


2.



B. γ-dihydro

1.



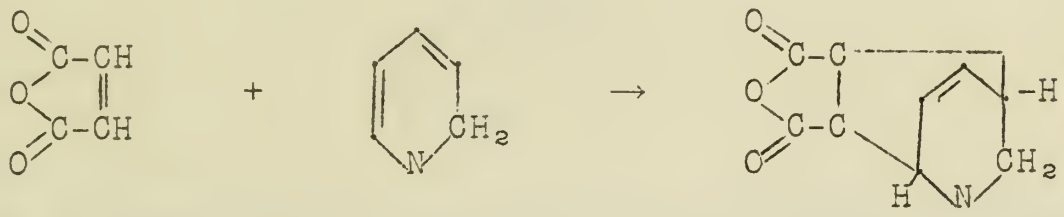
2, 3, 4. By thermal or acid disproportionation of tetrahydrodipyridyls; by Na·Hg reduction of the pyridine dimethyl sulfate addition product; by hydrogenation of the pyridine with Wislicenus activated aluminum as a catalyst.

Properties:

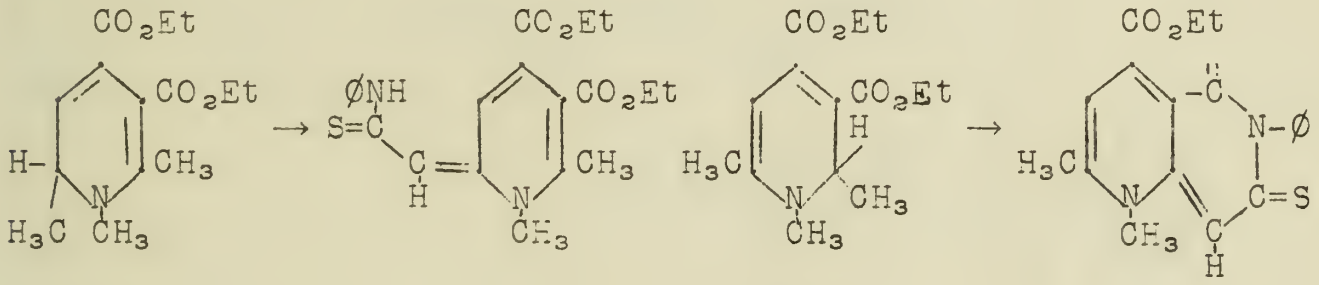
A. α-dihydro: 1. yellow color; 2. greenish-yellow, white, or negligible fluorescence; 3. more basic than other isomer; 4. stronger reducing agent; 5. takes up first two atoms of hydrogen rapidly on catalytic reduction, last two slowly; 6. usually not crystalline.

B. γ-dihydro: 1. colorless; 2. blue fluorescence; 3. weak base; 4. negative reducing action; 5. takes up first two atoms of hydrogen slowly on catalytic reduction, last two rapidly; 6. usually crystalline.

The structure of the compound obtained was proved by the method of preparation and the reaction of maleic anhydride in a Diels-Alder with the α-dihydro and not with the γ.



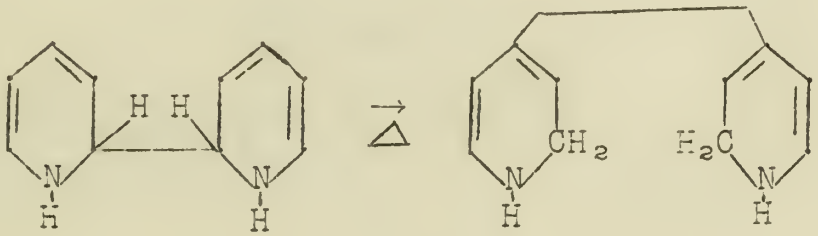
To determine the point of entry of the second hydrogen atom, N-methyl-α-dihydro-dimethyl cinchomeronic ester, where two isomeric structures are possible, was reacted with phenyl isothiocyanate. One isomer should react and ring close, the other should react and not ring close.

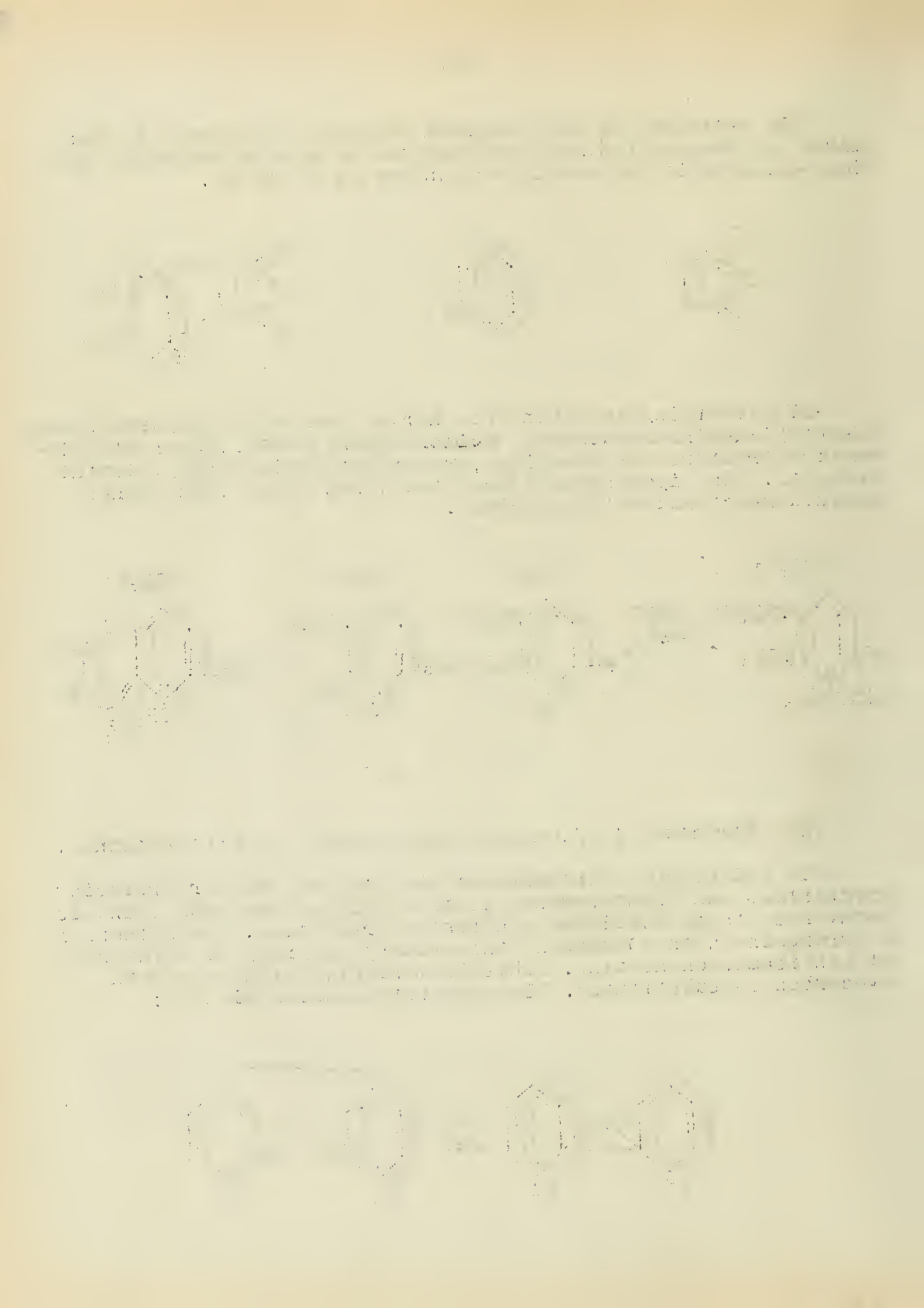


I II

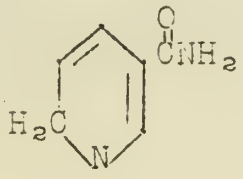
The structure is I, because ring closure is not obtained.

The bimolecular intermediate has the same color, reducing properties, and fluorescence as the α-dihydro compound, and is converted to the α-dihydro on further reduction. When there is a hydrogen on the γ carbon, the primary dipyridyl is converted to an isomer on heating. This isomerization fails when the γ-carbon is substituted. The suggested explanation is:



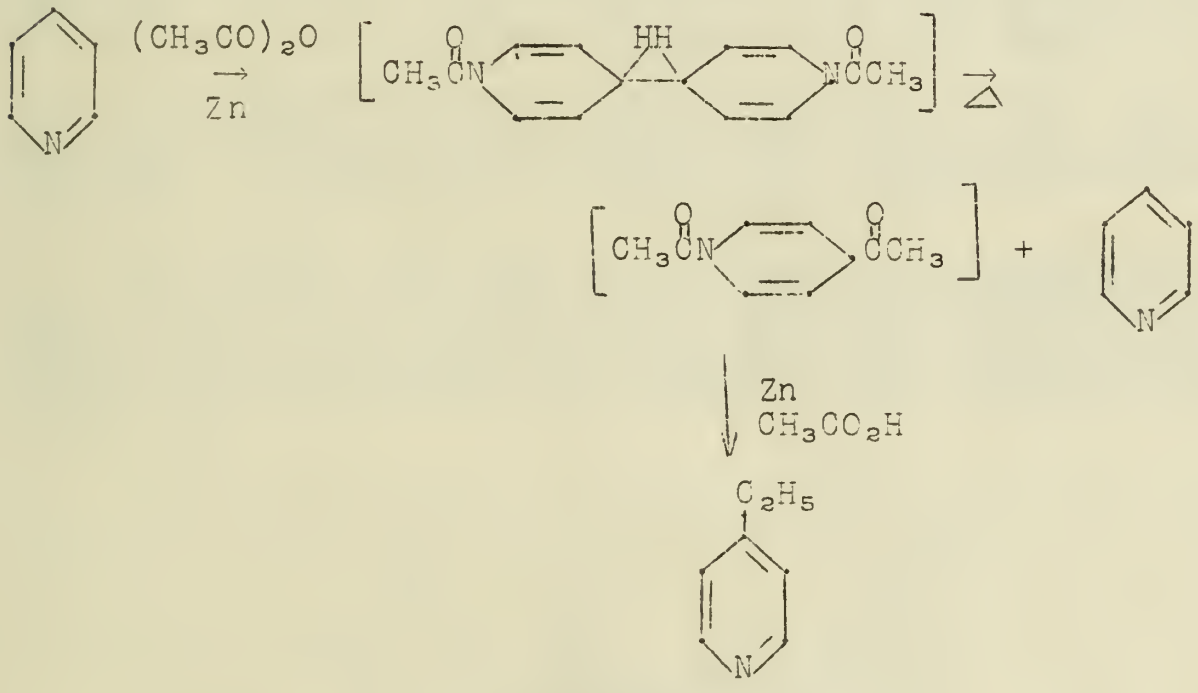


III. Conclusions.--In the reduced codehydrogenases, the nicotinic acid amide portion of the molecule has the structure:



The yellow intermediate in the reduction of cozymase is probably a tetrahydrodipyridyl.

Much of this chemistry is involved in a recent synthesis of 4-alkylated pyridines.



This procedure has been applied to other 4-alkylated pyridines.

Bibliography

Karrer, Helv. Chim. Acta, 19, 811 (1935).
Mumm, Ann., 538, 195 (1939).
Emmert, C. A., 14, 2794 (1920).
Arens and Wibaut, Rec. trav. chim., 61, 59 (1942).

Reported by David J. Wallace
March 7, 1947

TRIMERIZATION OF ACTIVE METHYLENE COMPOUNDS TO *sym*-TRISUBSTITUTED BENZENES

The self-condensation of three molecules of an active methyl or methylene compound to form a symmetrically substituted benzene has been used in a number of cases to prepare these compounds. A survey has been made to determine the usefulness of this reaction as a synthetic method.

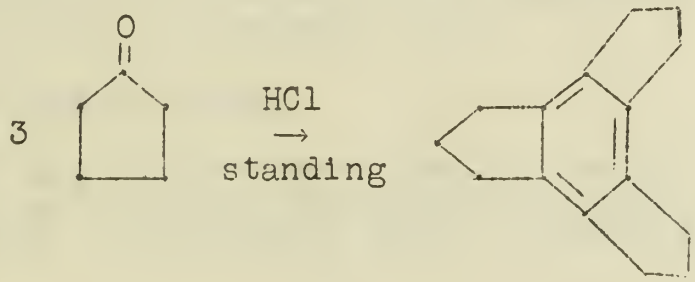
I. Condensations by Acids.

Condensations which are brought about by acids proceed through three successive aldol reactions, the last of which is an intramolecular one. The intermediates in this process have been isolated in a number of instances.

A. Alkylated Benzenes.--The simplest example of this reaction, the self-condensation of acetaldehyde to form benzene, has not been realized. Acetone, however, readily forms mesitylene with sulfuric acid; this is the standard preparation of this compound (1).

1,3,5-Triethylbenzene has been prepared in low yield by the action of sulfuric acid on methyl ethyl ketone (2). If crotonylene, $CH_3C{\equiv}CCH_3$, is shaken with sulfuric acid, hexamethylbenzene is formed; methyl ethyl ketone is also obtained (3).

The reaction has been used to synthesize symmetrical polycyclic compounds. The preparation of dodecahydrotriphenylene from cyclohexane in 10% yield is one example (4); another is the reaction of cyclopentanone with itself to form triscyclotrimethylenebenzene (5).



Truxene, tribenzylenebenzene, has been prepared by the self-condensation of both α-hydrindone (6) and phenylpropionic acid (7). There is no record of the use of β-hydrindone or the tetralones in this connection.

B. Arylated Benzenes.--The preparation of *sym*-triphenylbenzene from acetophenone (8) has been extended to various substituted acetophenones by Bernhauer, Müller and Neiser (9). These authors found that an *o*,*p*-directing group in the ring

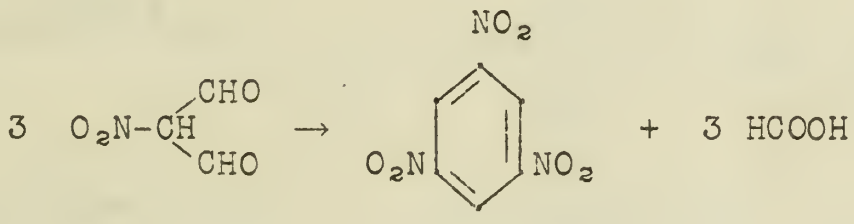
hinders reaction, while a m-director facilitates it. They also attempted to prepare hexaphenylbenzene from desoxybenzoin, but obtained tetraphenylfurane instead.

C. Acylated Benzenes.--Acetylacetaldehyde cannot be isolated as such; it condenses spontaneously to sym-triacetylbenzene in 40-50% overall yield (10). sym-Tripropionylbenzene (11) and sym-tribenzoylbenzene (12) have been made similarly, but in low yield.

More complicated molecules can be synthesized in this fashion (13, 14); the preparation of tribenzoylenebenzene, for example, can be accomplished by the use of any of several compounds (15).

D. Other Substituted Benzenes.--Malonaldehyde has been prepared (16), but there is no mention of its cyclizing to sym-benzenetrialdehyde.

Nitromalonaldehyde on standing gives a 20-24% yield of 1,3,5-trinitrobenzene (17).



The preparation of the triethyl ester of trimesic acid by the spontaneous self-condensation of formylacetic ester also illustrates this type of reaction (18).

II. Condensations by Bases.

The only base-catalyzed trimerization to form aromatic nuclei is the formation of sym-triphenylbenzene from acetophenone. Under these conditions the reaction takes a unique and interesting course.

After discovering in 1888 that acetophenone condensed with itself in the presence of potassium ethoxide, Delacre began an investigation of the structure of the intermediate compounds (19). By the action of alkali on acetophenone he obtained β-methylbenzalacetophenone or dypnone. This could be transformed into 1,3,5-triphenylbenzene as follows.

dypnone (I)

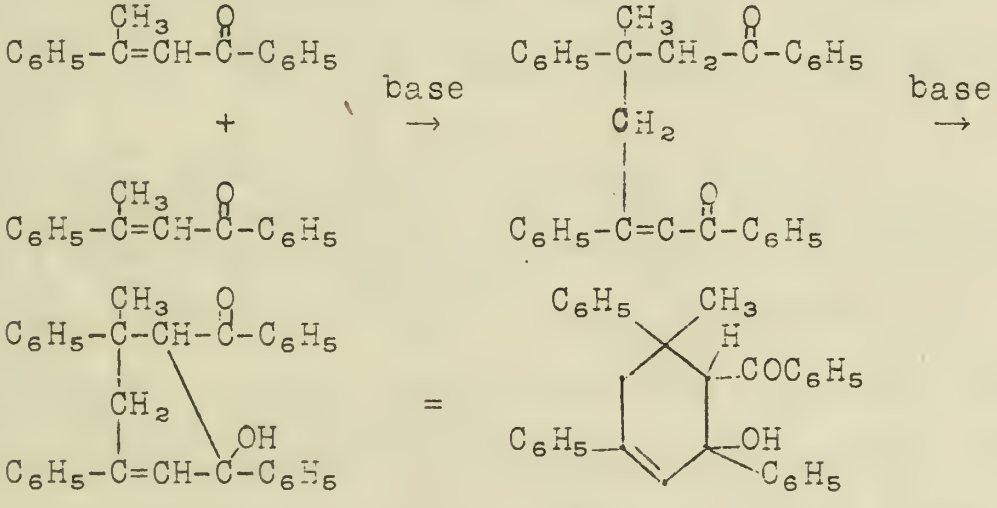
↓ base

"dypnopinacone"(II) (5 isomers) $\xrightarrow{-H_2O}$ "dypnopinacoline"(III) (9 isomers) $\xrightarrow[\text{or alkali}]{\text{acid}}$ "dypnopinalcolene" (IV)

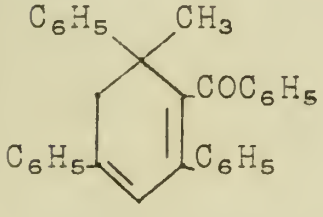
"dypnopinacoline" (III) ↓ △ → sym-triphenylbenzene + acetophenone

"dypnopinalcolene" (IV) ↓ mild oxidation → sym-triphenylbenzene

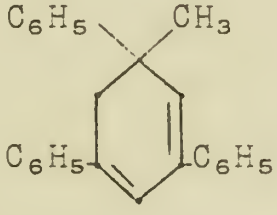
The structural formulas of these compounds were not known until 1943, when Ivanov and Ivanov obtained "dypnopinacone" by the self-condensation of dypnone in the presence of phenylmagnesylsodium acetate, $C_6H_5CH(MgCl)COONa$, and became interested in the problem of its structure. They were able to show (20) that the condensation consisted of a Michael reaction followed by a ring closure.



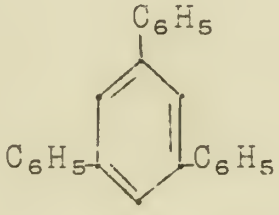
On this basis the other compounds were assigned the following structures.



"dypnopinacoline" (III)



"dypnopinalcolene" (IV)



sym-triphenylbenzene

These authors considered the various isomers of II and III to be either cis-trans isomers or polymorphic forms.

Bibliography

1. Organic Syntheses, John Wiley and Sons, N.Y., Collective Vol. I, p. 334 (1932).
2. Petrov, Ber., 60, 2548 (1927).
3. Almedingen, J. Russ. Phys. Chem. Soc., 13, 392 (1881); Ber., 14, 2073 (1881).
4. Mannich, Ber., 40, 158 (1907); Kunze, Ber., 59, 2086 (1926).
5. Wallach, Ber., 30, 1094 (1897).
6. Hausmann, Ber., 22, 2022 (1889); Kipping, J. Chem. Soc., 65, 278 (1894).
7. Kipping, J. Chem. Soc., 65, 278 (1894).
8. Knoevenagel and Goos, Ber., 55, 1934 (1922); Odell and Hines, J. Am. Chem. Soc., 35, 82 (1913).
9. Bernhauer, Müller and Neiser, J. prakt. Chem., (2), 145, 301 (1936).
10. Claisen and Stylos, Ber., 21, 1145 (1888); Varland, B.S. Thesis, U. of I. (1943).
11. Benary, Meyer and Charisius, Ber., 59, 108 (1926). Ashburn, B.S. Thesis, U. of I. (1943).
12. Claisen, Ann., 281, 306 (1894); Ashburn, B. S. Thesis, U. of I. (1943).
13. Landau, Ber., 33, 2440 (1900).
14. Kelber and Schwartz, Ber., 45, 2488 (1912).
15. Gabriel and Michael, Ber., 10, 1557 (1877); Michael, Ber., 39, 1910 (1906); Kostanecki and Laczkowski, Ber., 30, 2143 (1897).
16. Hüttel, Ber., 74, 1825 (1941).
17. Hill and Torray, Am. Chem. J., 22, 97 (1899); Ber., 28, 2598 (1895).
18. Reformatsky, J. Russ. Phys. Chem. Soc., 30, 280 (1898); J. prakt. Chem., 54, 477 (1896).
19. Delacre, Bull. Acad. Roy. Belgique, (3), 20, 466 (1888), et. seq.
20. Ivanov and Ivanov, Ber., 76, 988, 1148 (1943); ibid., 77, 173, 180 (1944).

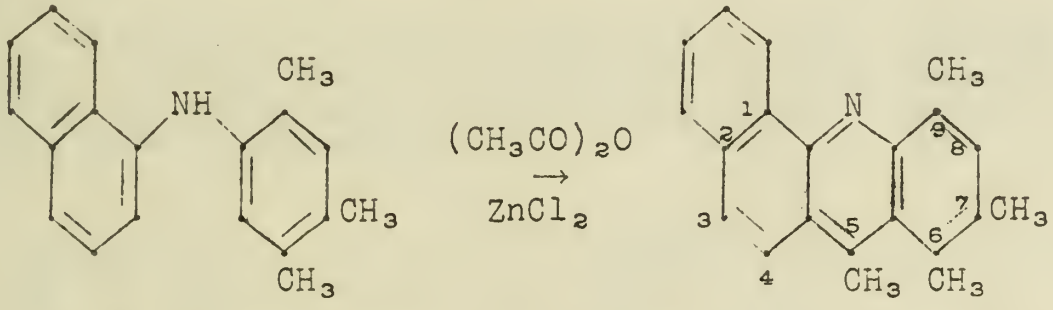
Reported by H. K. Hall
March 14, 1947

CARCINOGENIC NITROGEN COMPOUNDS

In somewhat more than a decade there have been discovered a number of polynuclear hydrocarbons which initiate the development of cancerous growths in human beings and experimental animals. Recent investigations of nitrogen compounds, both heterocycles and others, are of interest in this connection. The method of testing for carcinogenic activity consists of painting the skin with a benzene solution of the compound or of injecting subcutaneously a fatty suspension. Rats and mice are ordinarily used and may require an induction period of months before the appearance of a tumor is noted.

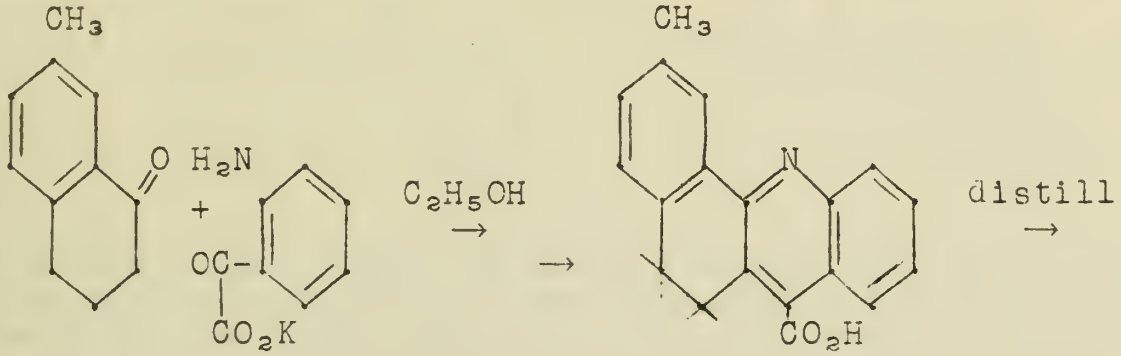
In the hydrocarbon series, 1,2,5,6-dibenzanthracene, 3,4-benzpyrene, and methylcholanthrene are particularly effective. Cholanthrene, 5,10-dimethyl-1,2-benzanthracene, and 10-methyl-1,2-benzanthracene are also active, so that it appears that 10-substitution is effective in the 1,2-benzanthracene structure, the parent hydrocarbon being completely inactive. The investigation of similar benzacridines has been carried out by Buu-Hoi and co-workers.

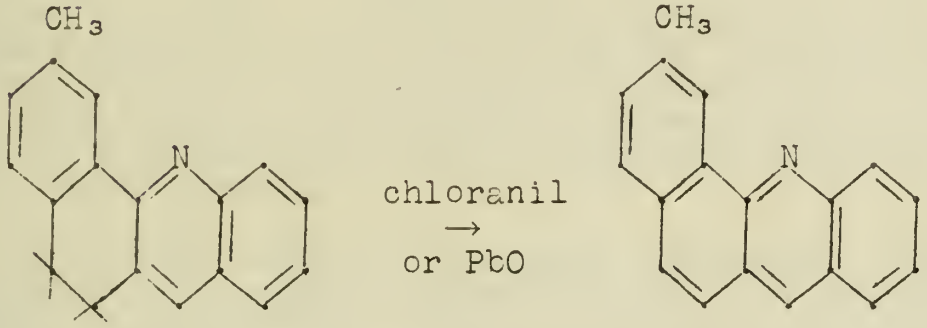
The Bernthsen reaction affords 5-substituted benzacridines. Thus N-pseudocumyl-α-naphthylamine heated with zinc chloride and acetic anhydride gives 5,6,7,9-tetramethyl-1,2-benzacridine, which has been found to be slowly active to give epithelioma (1).



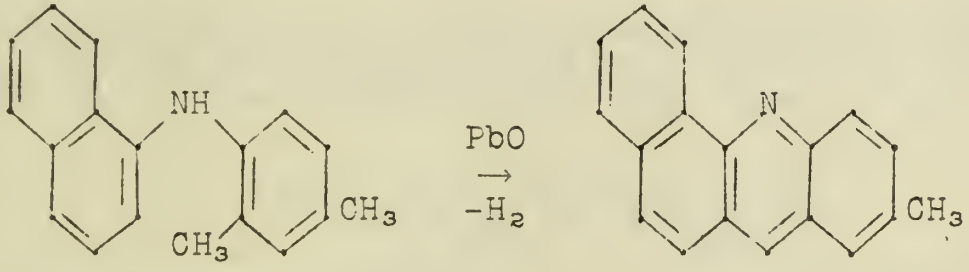
The corresponding β-naphthylamine gives 5,6,7,9-tetramethyl-3,4-benzacridine, which is also active. The amines required for these syntheses are conveniently prepared by heating the naphthol and substituted aniline with iodine at 200-210°. However, the Bernthsen reaction on the appropriate amines gave 2',5,9-trimethyl-3,4-benzacridine, 2',5,8-trimethyl-3,4-benzacridine, 8-chloro-5-methyl-3,4-benzacridine, and 9-chloro-5-methyl-3,4-benzacridine, all of which were inactive. Similar results were obtained with compounds which are similar to active meso substituted anthracenes. Both 3,5,7-trimethylacridine from di-p-tolylamine and 5-methyl-3,4,6,7-dibenzacridine from β,β-dinaphthylamine proved to be inactive. In general then, replacement of carbon by nitrogen results in diminution or loss of activity. A compound which approaches methylcholanthrene in activity is 5,8-dimethyl-1,2-benzacridine, prepared from N-m-tolyl-α-naphthylamine in the same manner (2). The 3,4-benzacridine from the β-naphthylamine is feebly active at best.

The absence of a methyl group in the 5- position may result in inactivity. 2'-Methyl-1,2-benzacridine is inactive. It may be prepared by means of the Pfitzinger-Borsche reaction, employing 7-methyl-1-tetrolone and potassium isatate (1,3).



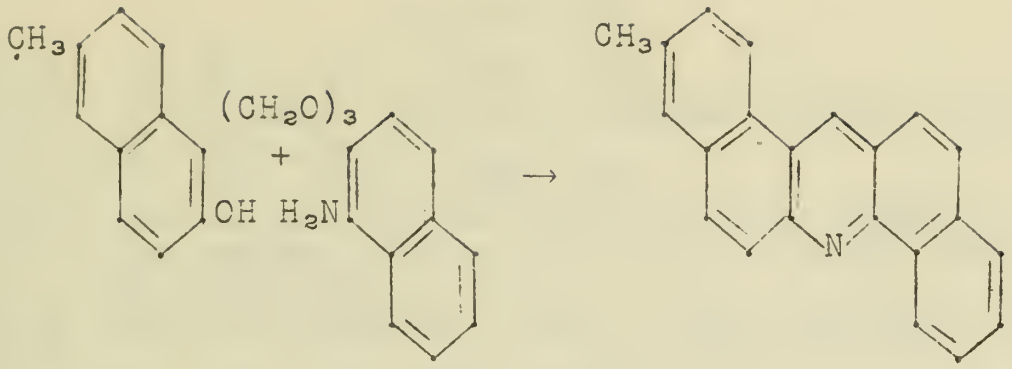


Substitution in the 7- position is still ineffective and 7-methyl-1,2-benzacridine is inactive. It was prepared from N-as-m-xylyl-α-naphthylamine by cyclodehydrogenation over lead oxide at elevated temperatures.



7-Bromo-2'-methyl-3,4-benzacridine and the corresponding chloro compound, prepared by the Pfitzinger reaction, were also found to be inactive.

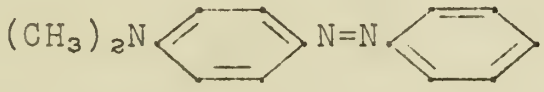
Similar results were obtained in an attempt to find active analogues of 3'-methyl-1,2,5,6-dibenzanthracene. The Ullmann-Fettvadjiian reaction, using 6-methyl-2-naphthol, α-naphthylamine, and trioxymethylene gave the inactive 3'-methyl-1,2,6,7-dibenz-acridine.



This lack of activity may not be as uninteresting as it may seem, since several such compounds show the unusual property of inhibiting the carcinogenic effect of very active compounds. For instance, 8,12- and 9,12-dimethyl-1,2-benzacridine retard the effect of methylcholanthrene if applied at the same time (5). Supposedly this action is due to competition between the two similarly constituted materials for position on the so-called cell "receptors." The specificity of this action is demonstrated by the fact that 7,9-, 7,11-, and 9,10-dimethyl-3,4-benzacridine and 7,9,11-trimethyl-3,4-benzacridine had no retarding action but indeed were active carcinogens.

In another series of nitrogen compounds, 1,2-benzcarbazole has pronounced carcinogenic properties (4). It is believed that this compound is responsible for the erroneous reports of activity in a number of hydrocarbons. However, N-alkylation destroys this activity. The methyl, ethyl, and propyl derivatives were prepared by treatment of the sodium salt of benzcarbazole with an alkyl halide (1). 3,4,5,6-Dibenzcarbazole produces sarcoma in mice (6).

Another series of nitrogen compounds which exhibit carcinogenic activity contain the azo group. Butter yellow has been recognized in this connection for some time.



Substitution in the benzene ring of this compound has interesting effects. A <u>para</u> methyl group causes little change in activity, but both the 2,4-dimethyl- and 3,4-dimethyl- compounds are inhibitors (7). The azotoluenes are also active, 4-amino-2,3'-azotoluene being even more carcinogenic than butter yellow, which is more effective than 4'-hydroxy-2,3'-azotoluene and 2,3'-azotoluene (8). Some alarm has been expressed at the use of such azo dyes as food colors.

Bibliography

1. Buu-Hoi, J. Chem. Soc., 1946, 792.
2. Buu-Hoi, Lacassagne, Lecocq, and Rudali, Compt. rend. Soc. Biol., 139, 955 (1945).
3. Buu-Hoi, J. Chem. Soc., 1946, 795.
4. Schürch and Winterstein, Z. Physiol. Chem., 236, 79 (1935).
5. Buu-Hoi, Lacassagne, Lecocq, and Rudali, Compt. rend. Soc. Biol., 139, 485 (1945).
6. Strong, Smith and Gardner, Yale J. Biol. and Med., 10, 335 (1938).
7. Nagao, Chem. Abs., 35, 6311 (1941).
8. Law, Chem. Abs., 35, 7525 (1941).

Reported by V. R. Gaertner
March 14, 1947

A NEW METHOD OF DISTINGUISHING COLORLESS COMPOUNDS IN CHROMATOGRAPHIC ADSORPTION

The techniques of chromatographic adsorption are applied to colorless as well as colored compounds. However it presents the problem of locating the zones of adsorbed material. In general the methods used may be classified as follows:

1. Empirical method
2. Use of indicators
   a. bursh technique
   b. internal indicators
   c. miscellaneous
3. Adsorption of colored derivatives
4. Detection under ultra-violet light.

A new method had recently been reported which appears to be more generally applicable than the above:

5. Adsorption on a fluorescent adsorbent.

In the empirical procedure the column is extruded and cut arbitrarily into sections. Each section is eluted and the resulting fractions are studied. Using this method Cassidy (1) succeeded in separating palmitic and stearic acids, which were identified by melting point after evaporation of the solvent. Walker and Mills (2) applied it to the study of the glycerides of linseed oil. The unsaturated fractions of oleic, linoleic and linolenic esters were distinguished by their iodine numbers.

The brush technique involves extrusion of the column, followed by painting a thin streak of indicator lengthwise on the column. The spots where coloration occurs mark the zones of adsorbed material. Zechmeister and coworkers (3) located α-naphthylamine adsorbed on calcium hydroxide by use of a solution of sodium nitrite and sulfanilic acid which caused a red coloration to appear. The following separations were also carried out; α-naphthylamine and benzidine, α-cyano cinnamamide and β-furfuryl-acrylamide using potassium permangante solution, cis- and trans-stilbene using permanganate solution, and cis and trans benzoin oxime as well as the anisoin oximes using an ammoniacal solution of copper sulfate (4,5). A zone of dimethyl glyoxime adsorbed on calcium hydroxide was located with a nickel sulfate solution, and Schiff reagent was used to detect benzaldehyde. Wolfrom and coworkers (6,7) applied the brush technique to sugars and related polyhydroxy compounds using potassium permanganate to locate the zones of adsorption. They thus separated d-glucose from sorbitol, d-mannitol from dulcitol, sucrose from raffinose, d-galactose from l-rhamnose, and a mixture of α-d-galacturonic acid, d-galactose, d-glucose, d-xylose, and l-rhamnose.

In come cases a small amount of indicator is adsorbed uniformly on the adsorbent prior to adsorbing the materials to be separated. This internal indicator method was used by Graff and Skan (8) to separate stearic from oleic and stearic from myristic acids. The adsorbent was magnesium oxide impregnated with phenolphthalein. Martin and Syng (9,10) reported a micro-analytical method for determining amino acids, using silica gel impregnated with methyl orange. Elsden (11), using bromocresol green as an

indicator, separated a mixture of formic, acetic, propionic, n-butyric and n-valeric acids. Sylvester and coworkers (12) used bromothymol blue on alumina to separate fatty acids from unsaponifiable oils.

Dyes may also be used in conjunction with other chromatographic methods. Bergdall and Doty (13) eluted a chromatogram of lysine, histidine and arginine into several fractions. The acids were determined in each fraction by specific dye tests.

Compounds to be separated are frequently converted to colored derivatives which are then chromatographed. Strain (14) first applied this method to the 2,4-dinitrophenylhydrazones of β-ionone and camphor as well as geronic acid and levulinic acid. Ladenburg and coworkers (15) separated cholesterol, stigmasterol and ergosterol by means of their p-azobenzenemonocarboxylic acid esters. Reich (16) and Coleman (17) used the same acid to separate sugar esters. The sodium salts of cholic and desoxycholic acids form esters with ω-bromo-p-methylazobenzene, which esters have been separated by adsorption on magnesium carbonate.

Many compounds which are colorless in daylight fluoresce under ultra-violet light. Thus the adsorbed zones of such compounds may be observed by exposing the column to ultra-violet. This method is called Ultrachromatography. Winterstein and coworkers (19) separated carbazole, naphthacene and anthraquinone from presumably pure anthracene. Similarly 1,2 benzcarbazole and naphthacene were separated from "pure" chrysene. Karrer and Nielson (20) and later Krasnova (21) studied the ultrachromatographic separation of cinchona alkaloids. Quinine and cinchonine were thus separated. It has been applied also to cholesterol and ergosterol. Nitro-substituted benzenes and naphthylenes (22) as well as tri- and tetramethylglucose (23) have been separated by this means.

Recently Brockmann and Volpers (24) reported a new method which should find more general application than the techniques mentioned above. It is based upon the fact that most compounds absorb light rays in the ultra-violet region. Thus if an adsorbent is used which fluoresces in the ultra-violet, the fluorescence will be partially or completely quenched by compounds adsorbed on its surface. A "negative chromatogram" will appear in which the zones of adsorption are seen as dark regions on a bright background.

Aluminum oxide is known to fluoresce under ultra-violet light when activated by small amounts of titanium dioxide, platinum or manganese (25). Alumina impregnated with diphenylfluorindinesulphonic acid, salicylic acid or the dye morin were found to cause the same effect. Of these, morin-alumina was the most suitable adsorbent. It showed a bright yellow fluorescence and had no effect on the adsorption-ability of the alumina.

The method was found to be successful in the separation of musk ketone, musk ambrette and xylene musk. The following mix-

tures were also separated using this technique: vanillin and piperonal, cinnamaldehyde and benzaldehyde, p-dimethylaminobenzaldehyde and benzaldehyde, mesityle oxide and phorone.

Other suitable adsorbents are berberine on silicic acid and calcium carbonate or magnesium oxide impregnated with morin or diphenylfluorindinesulfonic acid.

Brockmann and Volpers found the technique to be effective for compounds which absorb light in the range 250-400 mμ, which should make it suitable for most colorless compounds.

BIBLIOGRAPHY

General References

Zechmeister and Cholnoky, "Principles and Practice of Chromatography", John Wiley and Sons Inc., New York, 1943, p.79.
Strain, "Chromatographic Adsorption Analysis", Interscience Publishers Inc., New York, 1942, p.71.
Foerst, "Neuere Methoden der praparativen organischen Chemie", Verlag Chemie, G.M.B.H., Berlin, 1944, pp.560, 565.
Hesse, "Adsorptionsmethoden im chemischen Laboratorium", Edwards Brothers Inc., Ann Arbor, 1945, p.89.
Eliel, J. Chem. Education, 21, 583 (1944)
Strain, Ind. Eng. Chem. Anal. Ed., 14, 245 (1942)

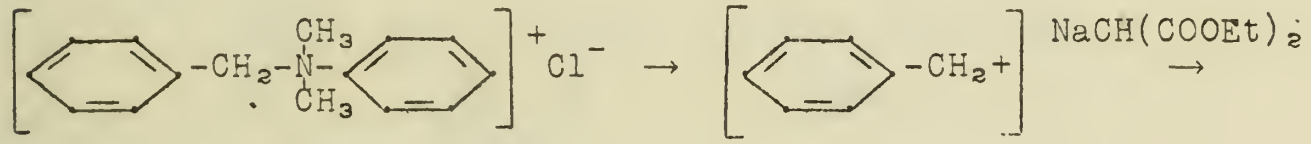
References

1. Cassidy, J. Am. Chem. Soc., 63, 2735 (1941)
2. Walker and Mills, J. Soc. Chem. Ind., 61, 125 (1942)
3. Zechmeister, Cholnoky and Ujhelyi, Bull. soc. chim. biol., 18, 1885 (1936)
4. Zechmeister, McNeely, and Solyom, J. Am. Chem. Soc., 64, 1922 (1942)
5. Zechmeister and McNeely, ibid., 1919 (1942)
6. Lew, Wolfrom, and Goepp, ibid., 68, 1449 (1946)
7. Georges, Bower, and Wolfram, ibid., 68, 2169 (1946)
8. Graff and Skan, Ind. Eng. Chem. Anal. Ed., 15, 340 (1943)
9. Martin and Syng, Biochem. J., 35, 1358 (1941)
10. Gordon, Martin, and Syng, ibid., 37, 79 (1943)
11. Elsden, ibid., 40, 252 (1946)
12. Sylvester, Ainsworth, Hughes, Analyst, 70, 295 (1945)
13. Bergdall and Doty, Ind. Eng. Chem. Anal. Ed., 18, 600 (1946)
14. Strain, J. Am. Chem. Soc., 57, 758 (1935)
15. Ladenburg, Fernholz, and Wallis, J. Org. Chem., 3, 294 (1938)
16. Reich, Biochem. J., 33, 1000 (1939)
17. Coleman and Farnham, Proc. Iowa Acad. Sci., 48, 246 (1941)
18. Silberman and Silberman-Martyncewa, J. Biol. Chem., 165, 359 (1946)
19. Winterstein, Schon , Vetter, Z. Physiol. Chem., 230, 158 (1934)
20. Karrer, Nielson, Ber. ges. Physiol. exp. Pharm., 86, 529 (1935)
21. Krasnova, J. Applied Chem., (U.S.S.R.), 18, 86 (1945)
22. Sinomiya, J. Chem. Soc. Japan, 61, 1221 (1940)
23. Norberg, Auerbach, Hixon, J. Am. Chem. Soc., 67, 342 (1945)
24. Brockmann and Volpers, Ber., 80, 77 (1947)
25. Tiede and Luders, Ber., 66, 1681 (1933)

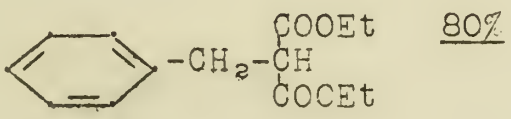
Reported by James B. McPherson Jr.
March 14, 1947

THE USE OF QUATERNARY MANNICH SALTS IN SYNTHESIS

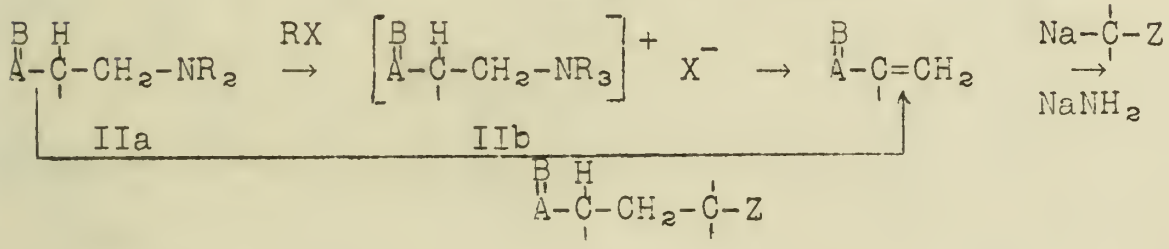
Dimethyl phenyl benzyl ammonium chloride (Ia) and the quaternary salts of Mannich Bases (IIb) are the only quaternary ammonium salts which have been used successfully in the alkylation of active methylene compounds (1-14). Mannich Bases and their quaternary salts decompose to form unsaturated compounds which can undergo the Michael Condensation in the presence of strong bases.



Ia Ib

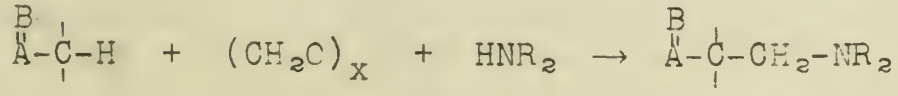


80%



Benzylation with (Ia) probably occurs via the carbonium ion (Ib) (9). A similar ion may be the active alkylating agent formed from quaternary Mannich Salts. The free Mannich Bases have also been used in this method of alkylation (15-17).

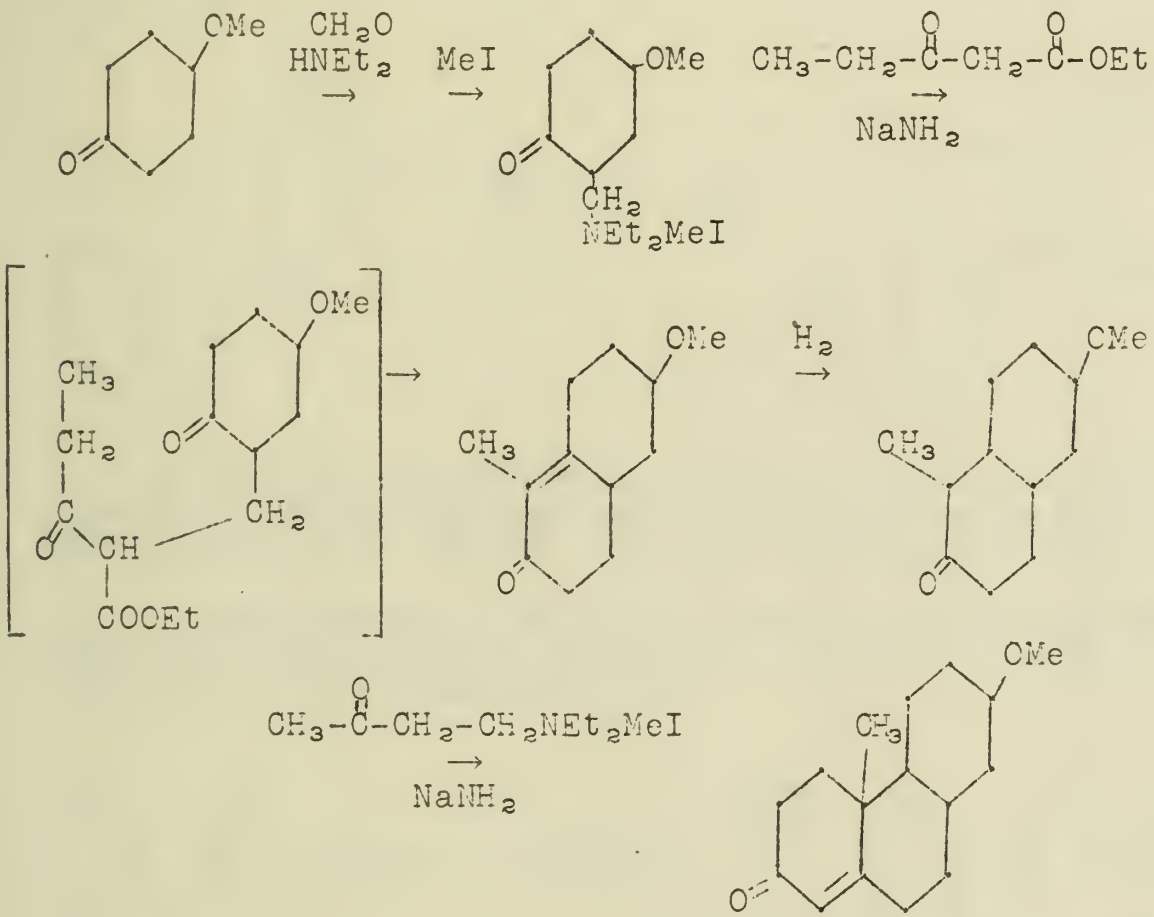
1. Scope.--The scope of this method of alkylation is not known, but probably any substance with the general structure (IIb) could be used. The Mannich Reaction (19) provides a convenient synthesis of compounds of type (IIa) from compounds with active hydrogen atoms, formaldehyde and a secondary amine.



IIa

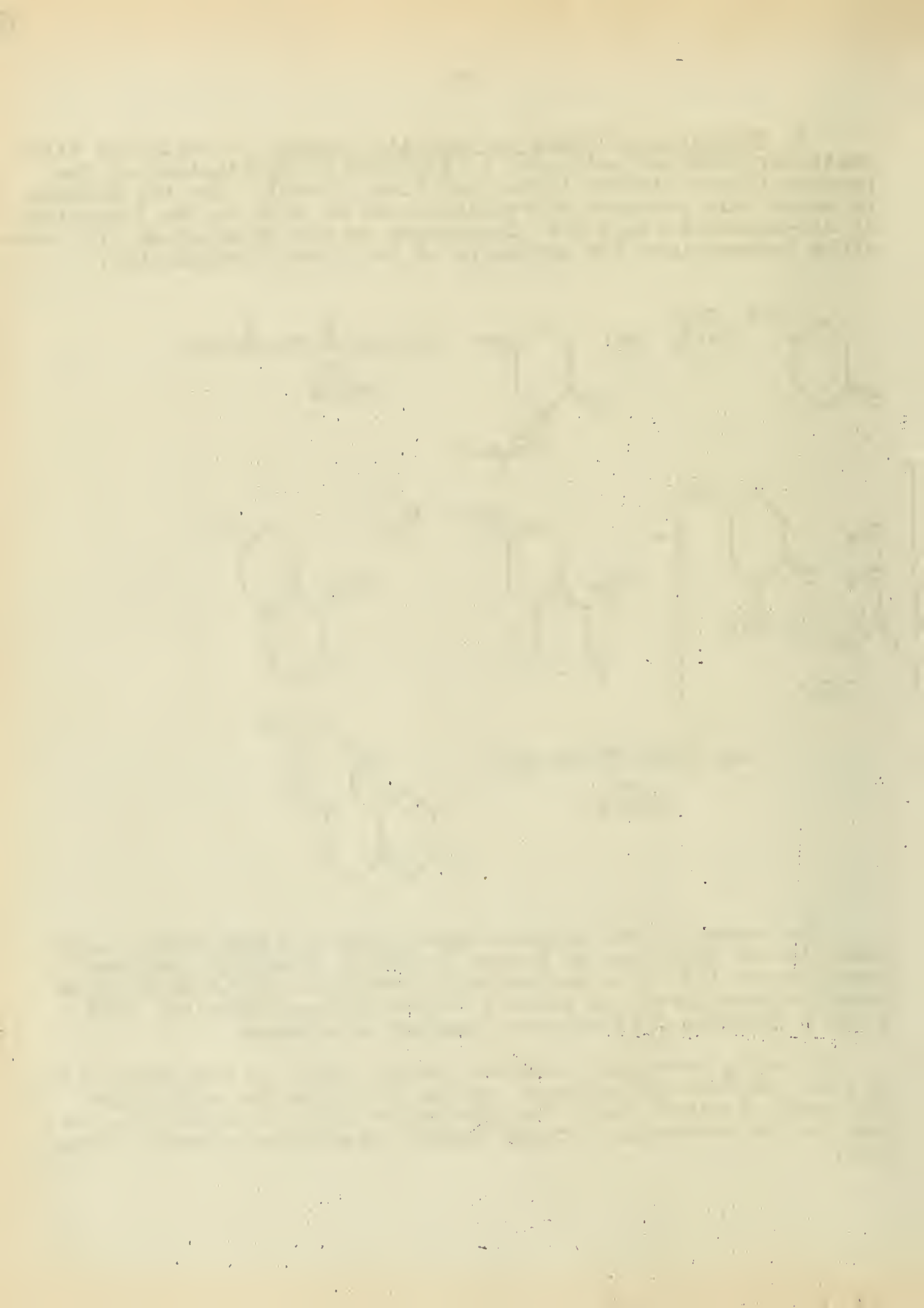
The Mannich Reaction has been applied to aldehydes, ketones, malonic, cyanoacetic and acetoacetic acids and esters, phenylacetylene, indole (19), pyrrole (18), aliphatic nitro compounds (23), ortho and para nitro derivatives of toluene (20), phenols (21) and halo-ketones (22). The only quaternary Mannich salts which have been used in alkylation are those derived from a few ketones and from indole.

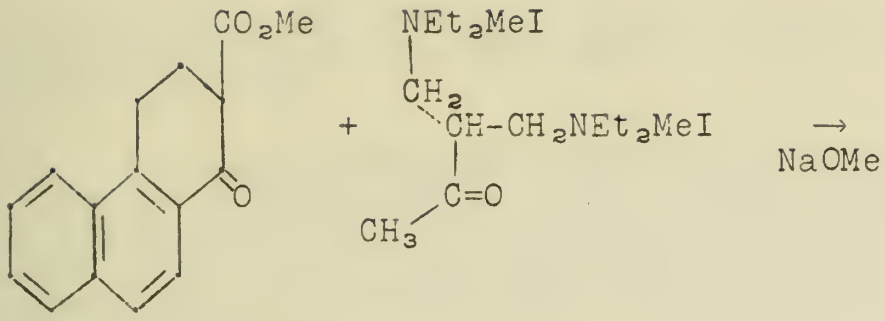
2. Synthesis of Fused Carbocyclic Systems.--Alkylation with quaternary Mannich salts can be followed by cyclization of the product (often without isolation) (1-8, 11-14). The two methods by which this sequence of reactions can be used in the formation of six-membered rings are illustrated in the preparation of a possible intermediate for synthesis of the sterol nucleus (5).

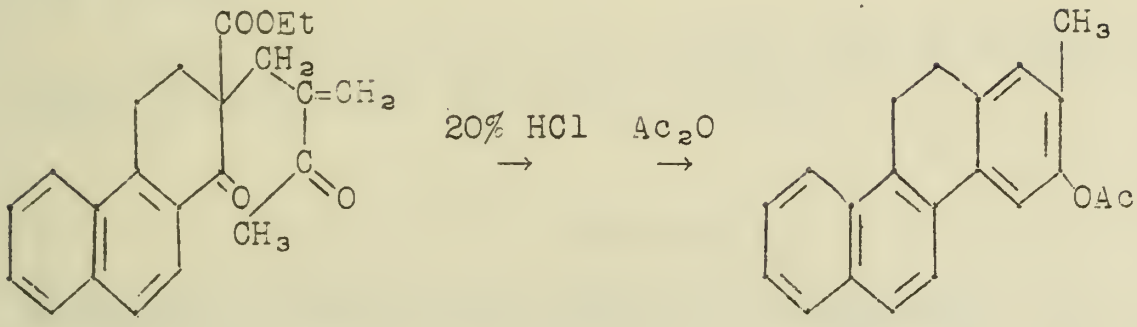


The second of the methods shown above has been most widely used; in the synthesis of 1-keto 7-hydroxy 13-methyl perhydrophenanthrene (8), of 3,4-dimethoxy 13--ethyl 5,6,7,8,9,10,13,14 octahydrophenathrene (a product derivable from thebaine) (12), α and β Cyperone (11) and many similar substances.

By using carefully purified Mannich Salts in the preparation of some chrysene derivatives, yields of 92% in the alkylation step were obtained (14). The di-Mannich Salt of acetone can be used in the synthesis of fused methyl substituted phenolic rings (14).

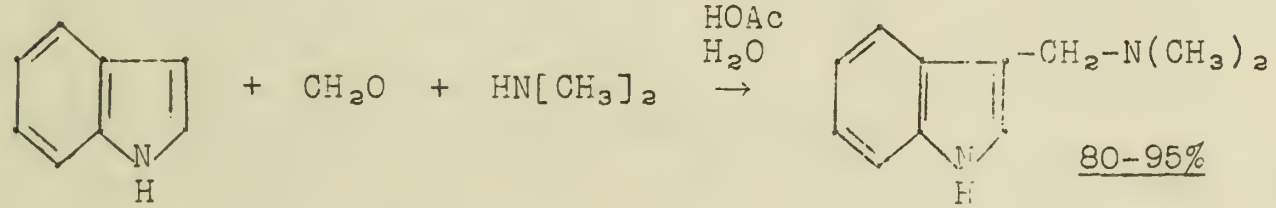


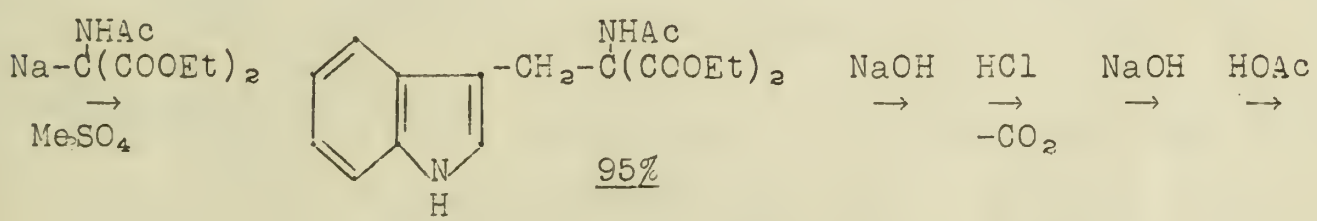


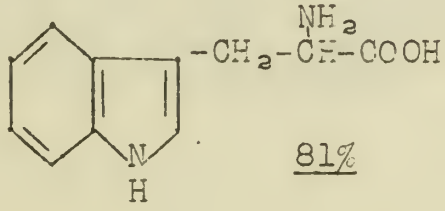


Morpholino Mannich Bases are more easily purified by crystallization than the simpler bases and their salts appear to be of about equal value in this type of alkylation (13).

3. Tryptophan.--The Mannich Base of indole (gramine) is an excellent alkylating agent (9) and has been used in a convenient synthesis of tryptophan (9-10).







Mannich Base and the sodio derivative of the active methylene compound results in a slow formation of the alkylating agent at low concentrations.

4. General Remarks.--This method is valuable in alkylation when the tertiary amine (IIa) is more readily available than the corresponding halide or activated olefin. Where comparisons have been made (1, 13), the quaternary Mannich Salt was shown to be the preferable alkylating agent, even when it had to be prepared from the halide.

A full evaluation of this method cannot be made until its scope has been more thoroughly studied.

Bibliography

Synthesis of Substances Related to the Sterols.
Robinson et al, (1) J. Chem. Soc., 1937, 53; (2) 1938, 1097; (3) 1938, 2001; (4) 1941, 386; (5) 1941, 391; (6) 1941, 582; (7) 1941, 586; (8) 1946, 676.

Synthesis of Tryptophan.
(9) Snyder, et al., J. Am. Chem. Soc., 66, 200, 350 (1944).
(10) Archer, et al., ibid., 66, 500 (1944); 67, 36 (1945); 68, 2105 (1946).

Other Uses of Quaternary Mannich Salts.
(11) Adamson, McQuillin, Robinson and Simonsen, J. Chem. Soc., 1937, 1576.
(12) Ghosh and Robinson, ibid., 1944, 506.
(13) Harradence and Lions, J. Proc. Roy. Soc., New South Wales, 72, 233, 273, 284 (1939).
(14) Wilds and Shunk, J. Am. Chem. Soc., 65, 469 (1943).

Alkylation by Means of Free Mannich Bases.
(15) Reichert and Posemann, Arch. Pharm., 275, 67 (1937).
(16) Mannich, et al., Ber., 70B, 355 (1937); 71B, 2090 (1938); 75B, 803 (1942).
(17) Howe, Zambito, Snyder and Tishler, J. Am. Chem. Soc., 67, 38 (1945).

The Mannich Reaction.
(18) Bachmann, G. B. and Heisey, J. Am. Chem. Soc., 68, 2496 (1946).
(19) Blicke, Organic Reactions, Vol. 1, p. 303.
(20) Bruson and Butler, J. Am. Chem. Soc., 68, 2348 (1946).
(21) Burckhalter, et al., ibid., 68, 1894 (1946).
(22) Land, Zeigler and Sprague, ibid., 69, 125 (1947).
(23) Senkus, ibid., 68, 1611 (1946).

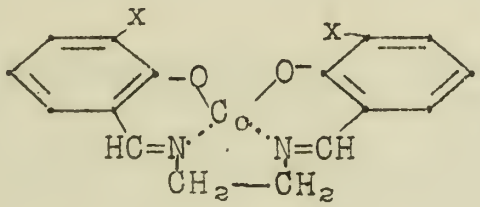
Reported by J. H. Brewster
March 21, 1947

OXYGEN-CARRYING SYNTHETIC CHELATE COMPOUNDS

Introduction.--Because of the importance of chelate compounds in biological oxidation-reduction reactions, Calvin began investigation of the previously known (3, 4) Compound I in 1938. This compound absorbs oxygen from the air. The oxygen may be driven off by heating. During the war, considerable research was carried out in developing compounds of this type to use in the preparation of pure oxygen from air.

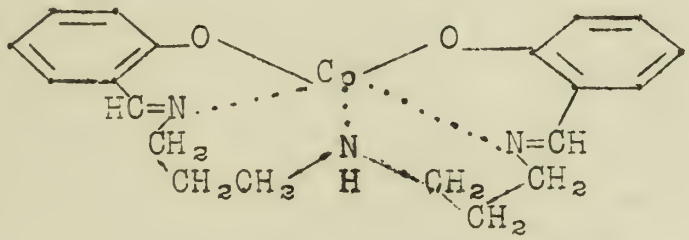
Preparation of Compounds.--Compound I was made by warming a solution of a cobaltous salt, salicylaldehyde and ethylene diamine in aqueous alcohol. Most of the other compounds studied were prepared analogously. A number of compounds were made with the objectives: (1) to increase the weight per cent of oxygen carried, (2) to increase the stability of the compound to irreversible oxidation, and (3) to increase the rate of oxygen absorption and release; all on the dry solid compound. Two types of compounds were found to be capable of carrying oxygen in the solid state. They are types A and B. Type A compounds may absorb one molecule of

Type A



Compound I, x = H
Compound II, X = F
Compound III, x = OEt

Type B



oxygen for each two atoms of cobalt, while type B compounds may absorb one oxygen molecule per cobalt atom.

Crystal Structure.--The activity of the solid compound is greatly dependent on its crystalline form and physical state. Some crystalline forms do not absorb oxygen. X-ray examination shows that in the active forms of Compound I, the molecules are so arranged as to leave holes in the crystal lattice large enough to accommodate oxygen molecules. In the inactive form, no such holes are present.

The Oxygenation Reaction.--The equilibrium oxygen pressure over several compounds of type A was measured at different temperatures and degrees of oxygenation. It was found, for example, that at 50% oxygen capacity, the oxygen pressure over Compound I was 5 mm. at 0° and 50 mm. at 25°, and over Compound II was 0.4 mm.

at 0° and 2 mm. at 25° (6). The pressure over solid type B compounds is considerably higher, but was not measured due to the slowness of reaction. A study of the reaction rates of type A compounds with oxygen showed a dependence on temperature. All compounds studied showed a temperature of maximum oxygen absorption, due to the fact that at increasing temperatures the reverse reaction, oxygen release, becomes important. It was found that the reaction is in all cases first order with respect to the oxygen pressure. With respect to the active chelate, the reaction was first order for Compounds I and III, and second order for Compound II. Compound II had the highest oxygenation rate of all of the compounds studied, being 80% saturated in 3.5 minutes at 25° and 151 mm. oxygen pressure.

Magnetic Measurements (8).--The magnetic susceptibilities of all of the active compounds of type A correspond to one unpaired electron per cobalt atom. Oxygen absorption causes the paramagnetic susceptibilities to decrease linearly to almost zero for the 100% oxygenated compounds. This shows that the addition compound has no unpaired electrons. The active type B compounds show three unpaired electrons per cobalt atom, decreasing to one at 100% oxygenation.

Oxygen Production (7).--The finely divided solid compound is placed in the inner tube of a heat exchanger which contains cooling water in the outer tube. Air is passed over the chelate for several minutes to provide oxygen, while the cooling water absorbs the heat of reaction. When the air current is stopped, steam is substituted for the cooling water in the outer tube. This causes the evolution of oxygen, which after a short "purging" period, is collected in a tank. When this is completed, the cycle may be repeated. Under these conditions, Compound I retained 70% of its activity after 300 cycles, while Compound II still had 60% activity after 1500 cycles. This corresponds to 130 lbs. of oxygen produced per lb. of Compound II deteriorated (or more than 40 liters per gram). The loss of activity is due to irreversible oxidation of part of the compound to products which poison the remaining material.

Oxygenation in Solution (10).--A series of measurements on type B compounds, usually in quinoline solution, showed that due to a high rate of deterioration, these compounds can not withstand very many oxygenation cycles. It seems that compounds with any desired oxygen saturation curve may be synthesized, including compounds capable of functioning as oxygen-carriers in aqueous solution.

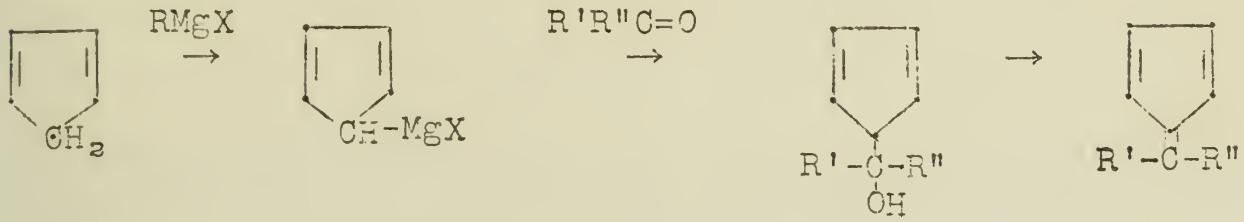
Bibliography

1. Calvin, Trans. Faraday Soc., 34, 1181 (1938).
2. Calvin, J. Am. Chem. Soc., 61, 2230 (1939).
3. Pfeiffer, Breith, Lübbe and Tsumaki, Ann., 503, 84 (1933).
4. Tsumaki, Bull. Chem. Soc. Japan, 13, 252 (1938).
5. Calvin, Bailes and Wilmarth, J. Am. Chem. Soc., 68, 2254 (1946).
6. Barkelew and Calvin, ibid., 68, 2257 (1946).
7. Wilmarth, Aranoff and Calvin, ibid., 68, 2263 (1946).
8. Calvin and Barkelew, ibid., 68, 2267 (1946).
9. Hughes, Wilmarth and Calvin, ibid., 68, 2273 (1946).
10. Harle and Calvin, ibid., 68, 2612 (1946).

Reported by Jack Hine
March 21, 1947

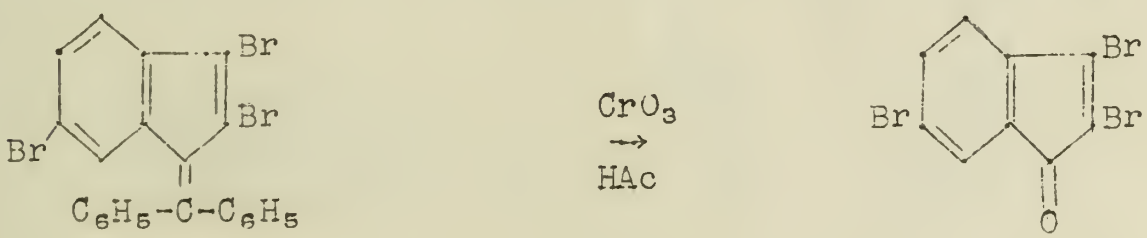
SOME REACTIONS OF FULVENES

Fulvenes are usually prepared from cyclopentadiene or its derivatives either by condensation with aldehydes or ketones in the presence of alkali, or by treatment with a Grignard reagent (1). Many of the highly arylated fulvenes have been prepared from arylated cyclopentadienones and the Grignard reagent (2).



Although fulvenes are chemically reactive, they do not rearrange to the isomeric benzene derivatives (3).

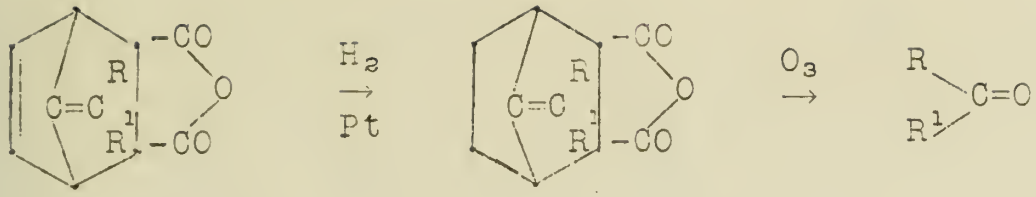
Halogenation.--The characteristic double bond of fulvenes does not add halogen. Substitution in the ring takes place instead (4). Diphenylfulvene with excess bromine gives the tetrabromofulvene. Controlled bromination of diphenylbenzofulvene rsults in the β-monobromo derivative. Halogenation in the α-position generally results in a deepening of color. The fact that the monobromo derivative is yellow is evidence that the fulvene double bond is not attacked. When two moles of bromine are used, the tribromo derivative (I) is isolated rather than the dibromo compound (5). Subsequent oxidation of the tribromofulvene results in 2,3,6-tribromoindone (II).



I II

Hydrogenation.--Hydrogenation of dimethyl and diphenylfulvene in the presence of platinum or palladium (6) in various solvents was studied (6). The first two moles of hydrogen are more readily absorbed than the third mole. In the case of dimethylfulvene, the addition of two moles of hydrogen gives a mixture consisting of 8% isopropylcyclopentane, 20% isopropylidenecyclopentane and 60% 1-isopropylcyclopentene.

Diene Synthesis.--Fulvenes undergo the diene-addition reaction (7) with maleic anhydride. Addition products with 6,6-dimethylfulvene, 6,6-diphenylfulvene and 6-styrylfulvene (III, R=R'=CH_3; R=R'=C_6H_5; R=C_6H_5CH=CH, R'=H) are obtained.



III

Similar addition products are obtained (8) from 6,6-tetramethylenefulvene and 6,6-petamethylenefulvene (III, R,R'= $-(CH_2)_4^-$ or $-(CH_2)_5^-$). The colorless crystalline adduct, although stable in the solid state, gradually assumes the color of the fulvene in ethyl acetate or benzene at room temperature. The development of color in solution was proven to be due to dissociation by detecting maleic anhydride in the solution and by freezing point determinations. The adducts were hydrogenated to the dihydro derivatives from which cyclopentanone and cyclohexanone were obtained on ozonization. This proves that the fulvene double bond was not hydrogenated and further that the structure of the adduct agrees with III.

The fulvene addition products, in general, dissociate into their components on solution in the cold.

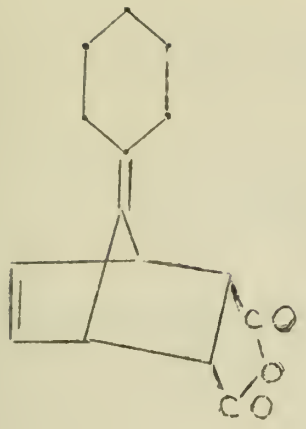
The reaction of fulvenes (9) with maleic anhydride is not stereochemically homogeneous, but leads, in many cases, to a mixture of products having different configurations.

Adduct with Maleic Anhydride in Benzene at 50-60°

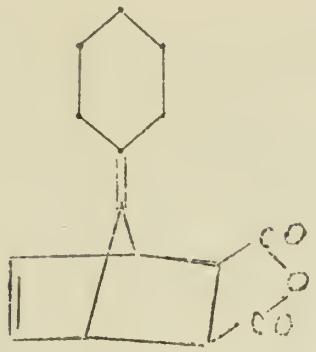
	% endo	% exo
Cyclopentadiene	100	0
Dimethylfulvene	40	60
Pentamethylenefulvene	40	60
Diphenylfulvene	0	100

The adduct formed from 6,6-pentamethylenefulvene and maleic anhydride (10) has been carefully studied. When the reaction is carried out in benzene solution at room temperature, the α-adduct is obtained. If, however, the mother liquor is allowed to stand for several weeks, a β-adduct gradually separates.

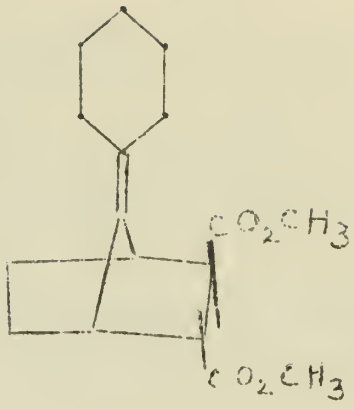
Proof of configuration of the α and β-adducts consists in hydrogenation to the dihydroanhydride followed by esterification from which is obtained an oil α-dihydrodimethyl ester and a crystalline β-dihydrodimethyl ester. Either dimethyl ester on boiling with sodium methoxide in methanol solution is inverted with the formation of the same transdihydrodimethyl ester (VI). The difference, therefore, between the initial α- and β-adducts is one of endo-exo isomerism.



(α) endo
IV

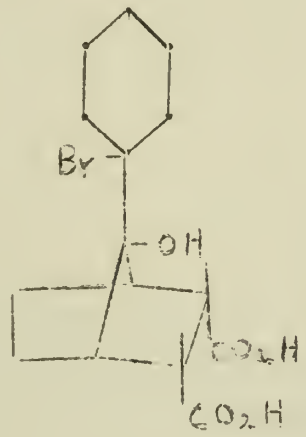


(β)exo
V

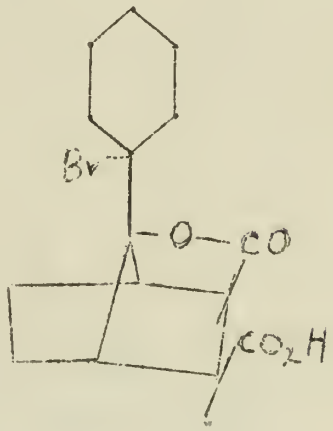


VI

On bromination of the α dihydroanhydride after long boiling with dilute acetic acid, a bromohydroxydicarboxylic acid (VII) is obtained. Similarly the β-dihydroanhydride gives a bromolactone monocarboxylic acid (VIII).

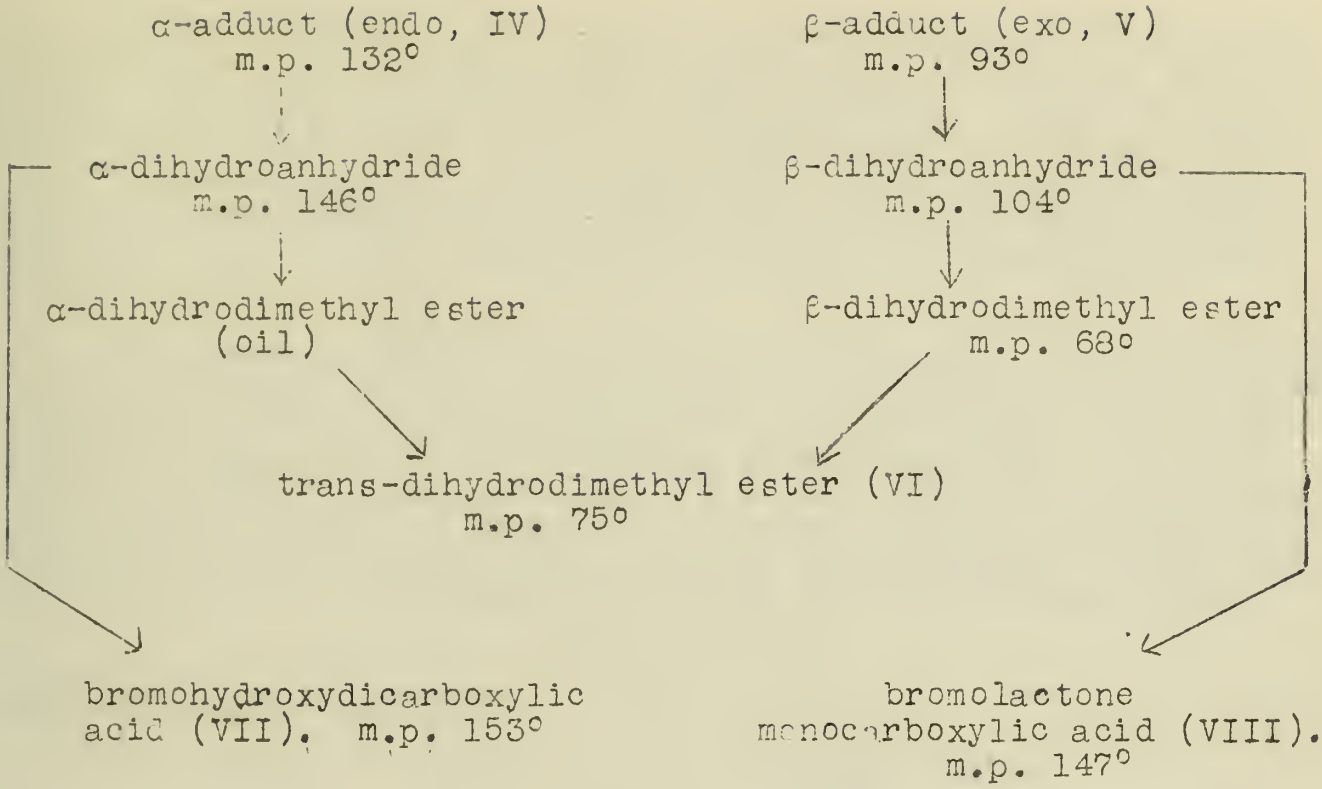


VII



VIII

Since only the exo carboxyls are suitably placed for lactonization involving the cyclohexylidene double bond, it is evident that the bromination products have the structure VII and VIII respectively and consequently, that the α series has the endo configuration while the β series are exo derivatives (the α-adduct has the structure IV and the β-adduct is to be formulated as V.



BIBLIOGRAPHY

1. Courtot, Ann. Chim., 4, 58 (1915).
2. Dilthey and Huchtemann, J. prakt. Chem., 154, 238 (1940).
3. Baker, J. Chem. Soc., 1945, 258.
4. Bergmann and von Christiani, Ber., 63, 2559 (1930).
5. Bergmann, Ber., 64, 1481 (1931).
6. Kazanskii and Tatevoysan, C.A., 33, 4204 (1939); 34, 5057 (1940).
7. Diels and Alder, Ber., 62, 2081 (1929).
8. Kohler and Kable, J. Am. Chem. Soc., 57, 917 (1935).
9. Alder and Stein, Angew. Chem., 50, 510 (1937).
10. Woodward and Baer, J. Am. Chem. Soc., 66, 645 (1944).

Reported by A. J. Speziale
March 21, 1947

o-NITROSOPHENOLS

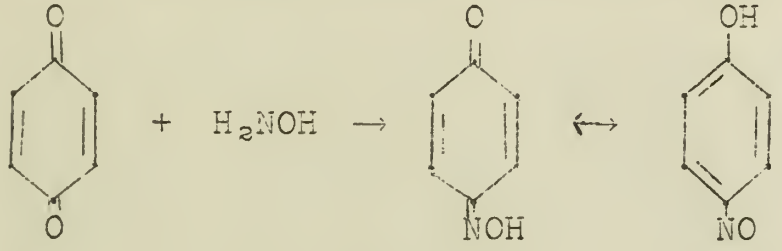
Prior to 1940, only a very few o-nitrosophenols were known. Bayer (1) first prepared o-nitrosophenol as its silver salt in 1893, but failed to isolate the free compound. Earlier investigations (2) had always led to the para isomer. Free o-nitrosophenol was prepared in 1912 by Baudisch and Karzeff (3), who further investigated the compound (4). More recently Hodgson (5) prepared 2-nitroso-5-aminophenol and the 2-nitroso-5-halogenphenols.

This small number of known o-nitrosophenols is due primarily to difficulties in their preparation. The action of nitrous acid on phenols leads to p-nitrosophenol although Viebel (6) found that the ortho isomer is formed as an intermediate. In 1940 Baudisch (7) (8) developed the use of the nitrosyl radical and an oxidizing agent to introduce a hydroxyl and a nitroso group simultaneously. This method has been improved upon by Cronheim (9) who used it to prepare over fifty new o-nitrosophenols.

METHODS OF PREPARATION:

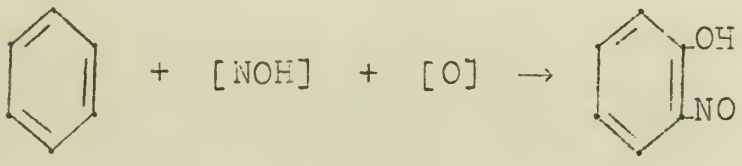
1. $C_6H_5OH + HCNO \rightarrow (p)\ NO\text{-}C_6H_4OH$ 80%

   The classical method leads to the para isomer unless the para position is already substituted.

2. 

   Only a very few nitrosophenols have ever been prepared by this method (2).

3. The Baudisch method (7):



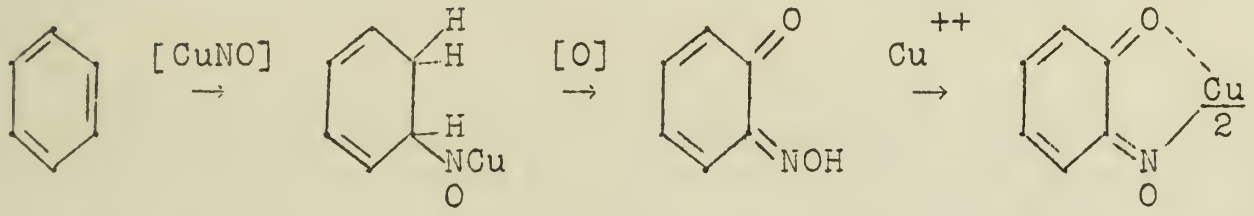
   When only the ortho isomer is desired, this method is most satisfactory. The nitrosyl radical is prepared in one of three ways.

   a. $H_2NOH.HCl + Cu^{++} \rightarrow [NOH] + Cu^{+}$

b. $HONO + Cu^{+} \rightarrow [NOH] + Cu^{++}$

c. $C_6H_5SONHOH + Cu^{++} + H_2O_2 \rightarrow [NOH] + Cu^{+}$

The cuprous ions (8) combine with the nitrosyl radical to form a complex of the type [CuNO]Cl which is more stable than the nitrosyl radical itself. This complex is paramagnetic indicating that the NO group has one unpaired electron. The electron attacks an ethylene grouping in the benzene ring and the intermediate is then oxidized to the o-quinone thereby breaking the bond between the copper and nitrogen. The o-quinonemonoxime forms at once an inner complex salt which is very stable and prevents further oxidation to o-nitrophenol or rearrangement to p-nitrosophenol.



No reaction occurs unless the pH is carefully controlled. The free o-nitrosophenol can be liberated from the complex by acid treatment and extraction with ligroin.

The reaction also can be applied to phenol and substituted phenols. Even if the benzene ring contains two substituents either of the same or of different kinds, it is possible to introduce a hydroxyl and a nitroso group by means of the Baudisch reaction. Amines and aldehydes do not react properly, but give the diazo compound and the hydroxamic acid or oxime respectively. In the case of alkyl benzenes, it has been shown (8) that the nitroso group enters the ring as far as possible from the alkyl group.

PROPERTIES:

Free o-nitrosophenols form very volatile light green crystals soluble in most organic solvents. In the presence of water they shift to the brown o-quinonemonoxime. Their most characteristic behaviour is the formation of highly colored inner complex salts with heavy metals. The affinity for several metallic ions is so strong that it is sufficient to shake a solution of the free o-nitrosophenol in petroleum ether with an aqueous salt solution to form immediately and quantitatively the corresponding o-nitrosophenol complex (10). The affinity differs greatly, however, depending on the heavy metal.

TABLE I

1. Metals with great affinity:

Cu^{++}, reddish-violet; Hg^{++}, reddish-violet; Ni^{++}, red; Fe^{++}, green; Co^{++}, grayish-violet; Pd^{++}, green.

2. Metals with medium affinity:

Zn^{++}, pink; Pb^{++}, pink.

3. Metals with little affinity:

Fe^{+++}, brown; Ag^{+}, Au^{+++}, Cd^{++}, Mn^{++}; Uranium, red.

The solubilities of these complexes vary somewhat, although certain rules have been formulated (9). Those of cobalt, palladium and trivalent iron are soluble in petroleum ether and ether and are insoluble in water, while those of copper, mercury, nickel and divalent iron are soluble in water and/or ether and are insoluble in petroleum ether.

Substituted o-nitrosophenols have the same properties as o-nitrosophenol. Their salts, although similar, are not absolutely uniform. Usually the difference lies not in the type of the other group, but in where it is substituted with respect to the o-nitrosophenol grouping. Cobalt is unique in that all the complexes from ortho substituted o-nitrosophenol are grayish-violet, while those from meta and para substituted o-nitrosophenol are reddish-brown. This property has been used to determine the point of substitution in many new compounds.

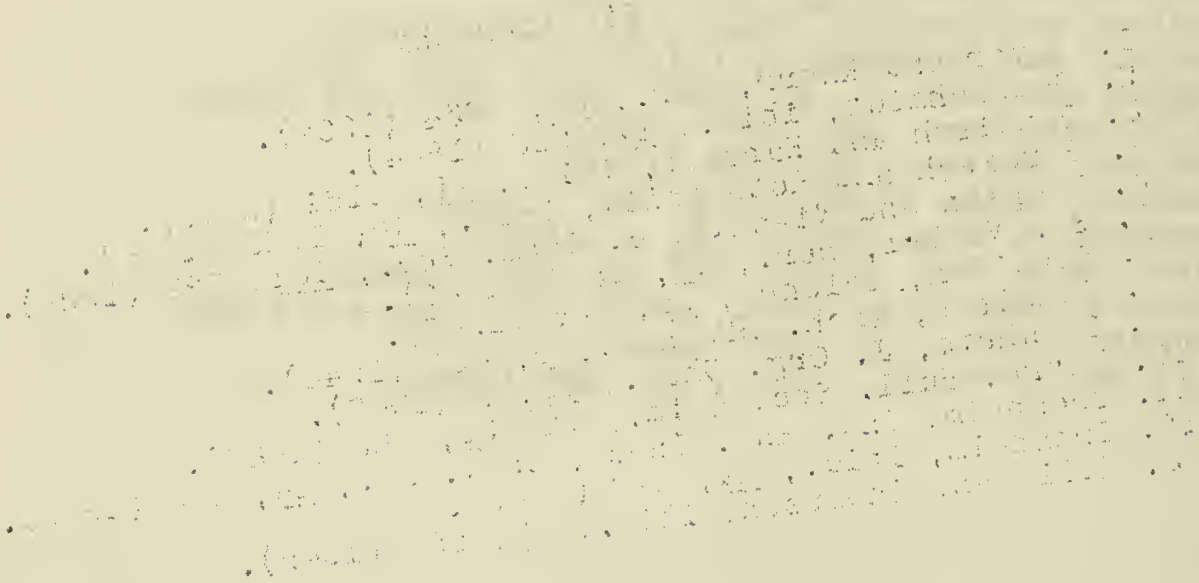
APPLICATIONS:

Since certain metals possess a great affinity for o-nitrosophenols, they have been utilized in developing new techniques for the colorimetric analysis of metals. As early as 1883, Fevre (10) had noted that o-nitrosoresorcinol could detect the ferrous ion even in a dilution of one part in ten million. Recently, Cronheim (11) (12) developed a satisfactory technique for the colorimetric estimation of cobalt and iron. Using o-nitrosophenol, estimations of five micrograms in fifty milliliters can be made with an error not exceeding one per cent. Ellis and Thompson (13) devised a scheme for the colorimetric estimation of cobalt in biological material using o-nitrosocresol, since the latter is easier to make and gives more intense colors than o-nitrosophenol.

Bibliography

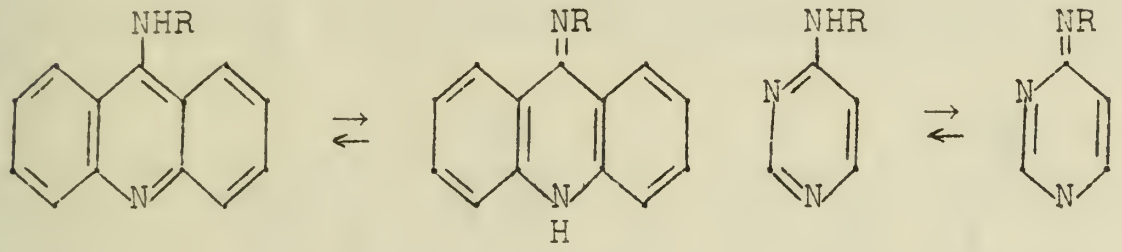
1. Bayer and Knorr, Ber., 35, 3034 (1902).
2. Goldschmidt, ibid., 17, 213 (1884).
3. Baudisch and Karzeff, ibid., 45, 1164 (1912).
4. Baudisch and Rothschild, ibid., 48, 1660 (1915).
5. Hodgson and Wignall, J. Chem. Soc., 131, 329 (1928).
6. St. Viebel, Ber., 63, 1577 (1930).
7. Baudisch, Science, 92, 336 (1940).
8. Baudisch, Arch. Biochem., 5, 401 (1944).
9. Cronheim, J. Org. Chem., 12, 1 (1947).
10. Fevre, Bull. Soc. Chim., (2) 39, 585 (1883).
11. Cronheim, Ind. Eng. Chem., Anal. Ed., 14, 445 (1942).
12. Cronheim, ibid., 14, 447 (1942).
13. Ellis and Thompson, ibid., 17, 254 (1945).

Reported by F. N. Baumgartner
March 28, 1947



PALUDRINE (A NEW ANTIMALARIAL DRUG)

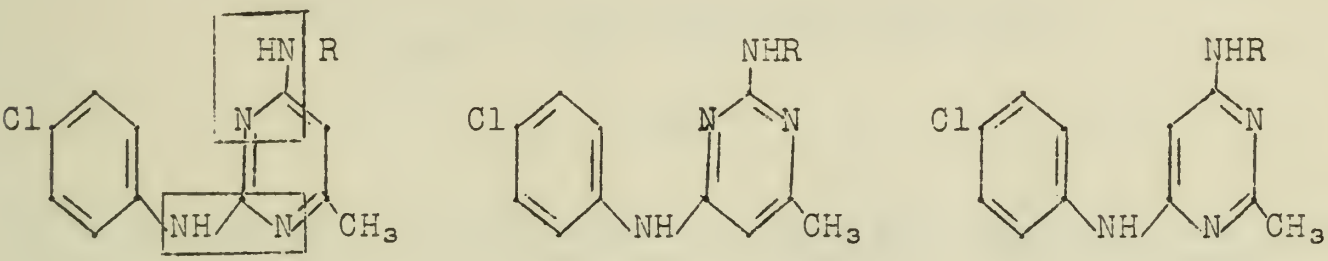
The suggestion was made that the antimalarial properties of atebrin are connected with the tautomeric possibility which exists in the molecule.[1]



I II

R = $CH(CH_3)(CH_2)_3N(C_2H_5)_2$

Dialkylaminoalkylamino pyrimidine derivatives represent an analogous tautomeric system (I), (II). Among the derivatives of pyrimidine the three following compounds were tested as possible potential antimalarials. Of these three (III) and (IV) were found



III IV V

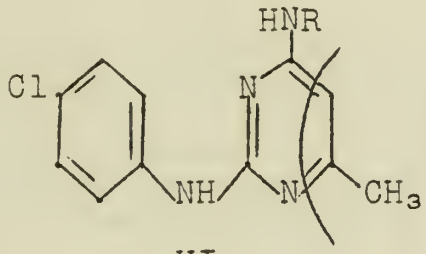
R = $(CH_2)_2N(C_2H_5)_2$

to be active whereas (V) was entirely devoid of activity. A close examination of types of (III) and (IV) shows that p-quinonoid structure is only possible in the former, yet both provide active substances.

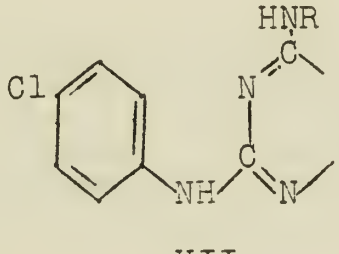
Curd and Rose[2] tentatively modified Schönhöfer's hypothesis to embrace tautomerism leading to an o-quinonoid and that, in the pyrimidine series, antimalarial activity might be expected when both arylamino and dialkylamino substituents were present each of which permitted the formulation of either o- or p-quinonoid like tautomers.

However, the inactivity of the isomeric type (V) called for some modification of this generalization and it was further postulated that the tautomeric systems associated with the substituent arylamino and alkylamino groups should be capable of independent

function. If, therefore, the structural requirements for antimalarial activity were indeed two linked and yet independent amidine systems , as indicated in (III), it suggested that the pyrimidine ring might not be essential and omission of the carbon atoms in positions 5 and 6 of the pyrimidine ring was indicated. This left the skeleton of which the central portion was seen to be duplicated in the biguanide system. Compound (VIII) was,

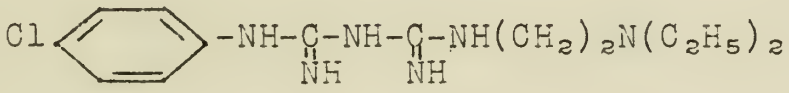


VI



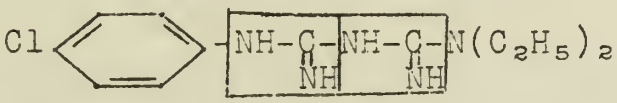
VII

amongst other biguanide derivatives, examined for antimalarial activity and was found to be inactive. Owing to the high basicity



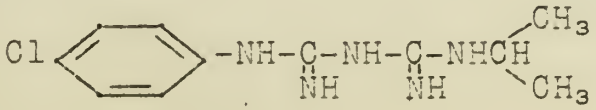
VIII

of this compound, it was decided to omit the $-NH(CH_2)_2-$ unit to give (IX) which as indicated still contained two independent



IX

amidine systems. Antimalarial activity was restored and variation of the terminal alkyl groups led to the discovery of (IX) which was the first compound of the biguanide type to undergo clinical trial. It proved to be active in human malaria[3] but was soon superseded by the more active 4888 (Paludrine) (X).

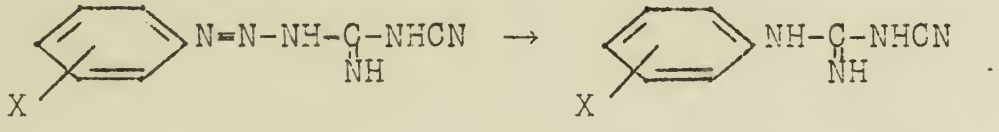


X

On laboratory tests this substance appeared to be unique among antimalarial substances and to hold out the possibility for the first time of true prophylaxis in malaria.

Synthesis of diguanides.--The most convenient starting material for diguanides of the type (IX) has been dicyandiamide. The interaction of dicyandiamide with ammonium chloride yields diguanide hydrochloride.[4] This reaction has been extended to aryl and alkyl amines.[5]

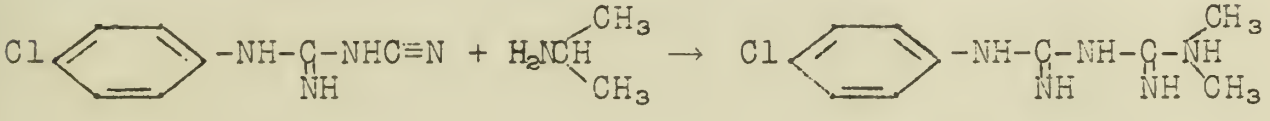
The parent p-chlorophenyl diguanide corresponding to (X) was made[2,6] by reacting p-chloroaniline hydrochloride with dicyandiamide. Also phenyl dicyandiamide gives an analogous compound from phenyl isothiocyanate and sodium cyanamide.[7] Passing of dry hydrogenchloride into an ether suspension of a compound represented by (IX) is another approach for the preparation of such compounds.[8]



XI XII

Compound (XI) was prepared in good yields by coupling diazotized p-chloroaniline with dicyandiamide in aqueous sodium carbonate. It is dangerous to handle this substance (XI) in bulk when dry, since it is readily detonated by friction. The more stable wet filter paste from the coupling reaction is decomposed smoothly and cleanly into (XII) by addition to a mixture of concentrated HCl and a water miscible solvent, such as β-ethoxyethanol, acetic acid or acetone.

The aryl dicyandiamides have been converted into diguanides by interaction with either the amine hydrochloride or the amine in the presence of copper sulphate. Thus Paludrine or N_1-p-chlorophenyl-N-isopropyl biguanide was prepared from p-chlorophenyl dicyandiamide (XIII) and isopropyl amine.



XIII Paludrine

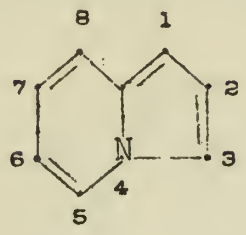
Bibliography

1. Schönhöfer, Z. Physiol. Chem., 124, 1 (1942).
2. Curd and Rose, J. Chem. Soc., 729 (1946).
3. Adams, Ann. Tro. Med., 39, 217 (1945).
4. Bamberger and Dieckmann, Ber., 25, 545 (1892).
5. Smolka and Friedreich, Monatash., 9, 228 (1888).
6. Strukov, Sychra and Simirnov, J. Chem. Ind. U.S.S.R., 18, 22 (1942).
7. Wheeler and Jamieson, J. Am. Chem. Soc., 25, 719 (1903).
8. Walther and Grieshammer, J. Prakt. Chem., 92, 251 (1915).

Reported by N. Shanmukha Rao
March 28, 1947

THE CHEMISTRY OF THE PYRROCOLINES

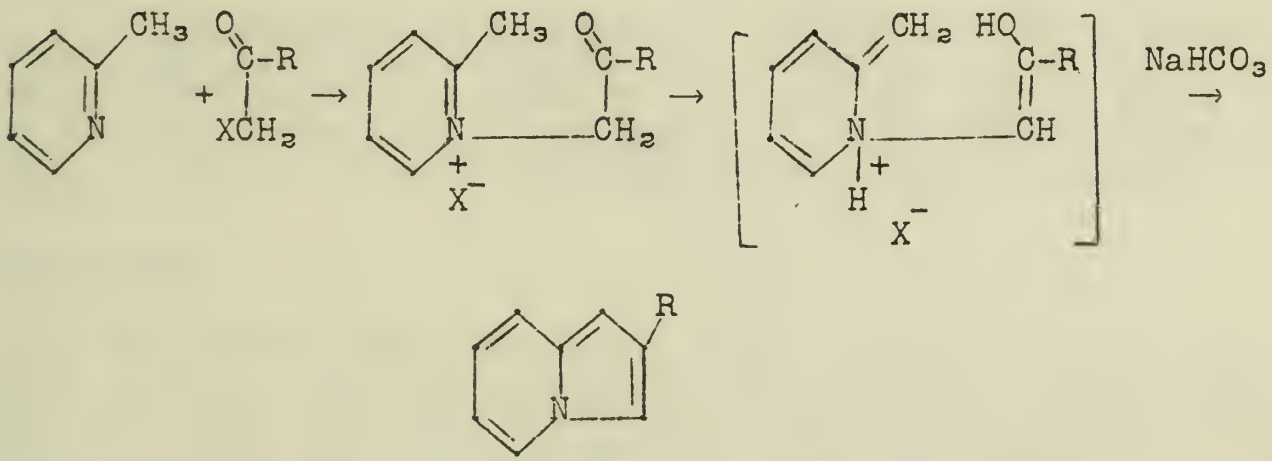
The pyrrocoline ring system is shown by the following formula.



The names pyrindole and indolizine and other numbering systems have also been employed.

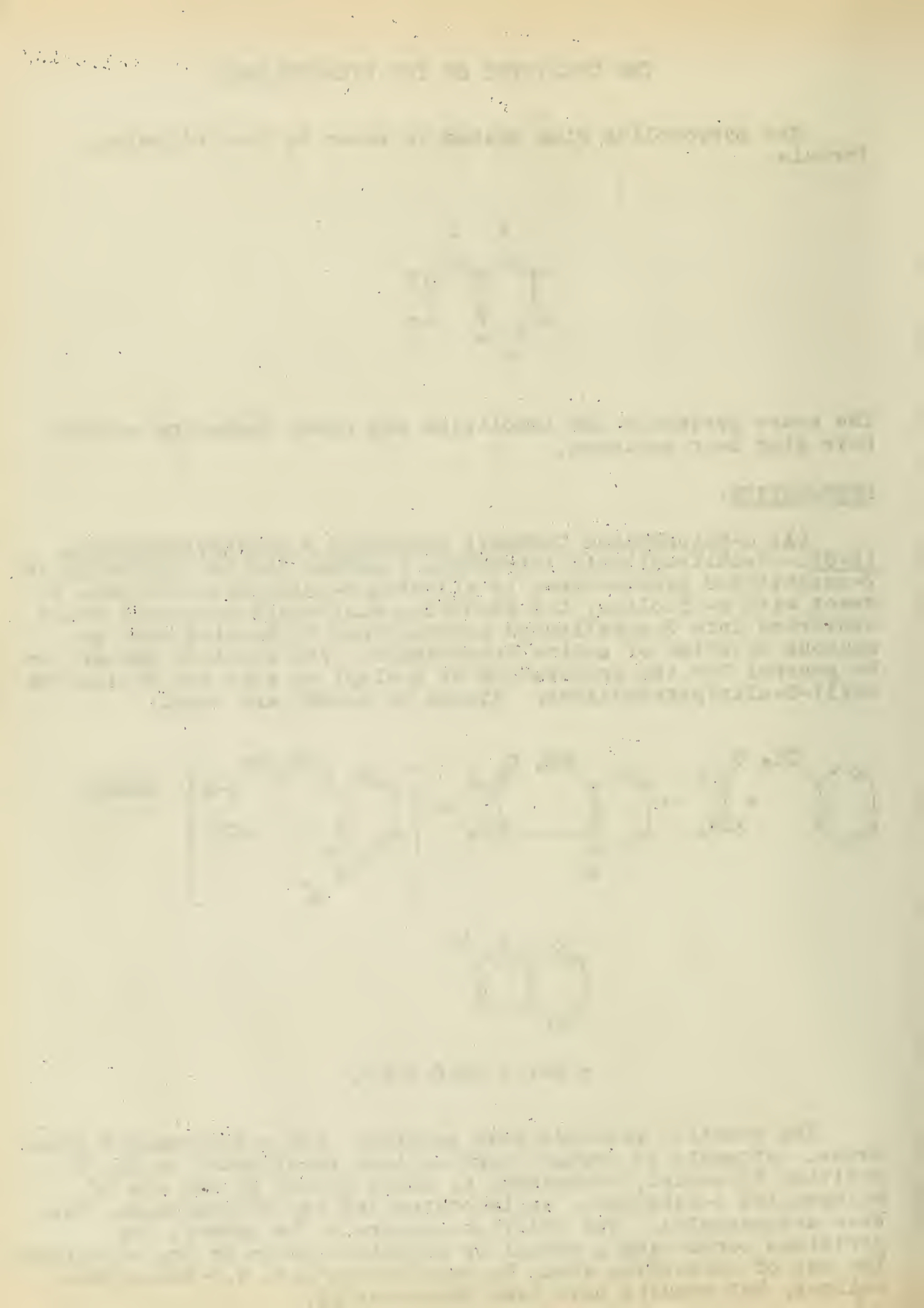
PREPARATION:

(1) α-Halogenated Carbonyl Compounds + α-Methylpyridines (1-5).--Tschitschibabin introduced a method for the synthesis of 2-substituted pyrrocolines by allowing α-halogenated ketones to react with α-picoline, the resulting quaternary compounds being converted into 2-substituted pyrrocolines by heating with an aqueous solution of sodium bicarbonate. The reaction appears to be general for the preparation of 2-alkyl or aryl and 2-alkyl(or aryl)-3-alkylpyrrocolines. Yields of 40-80% are usual.

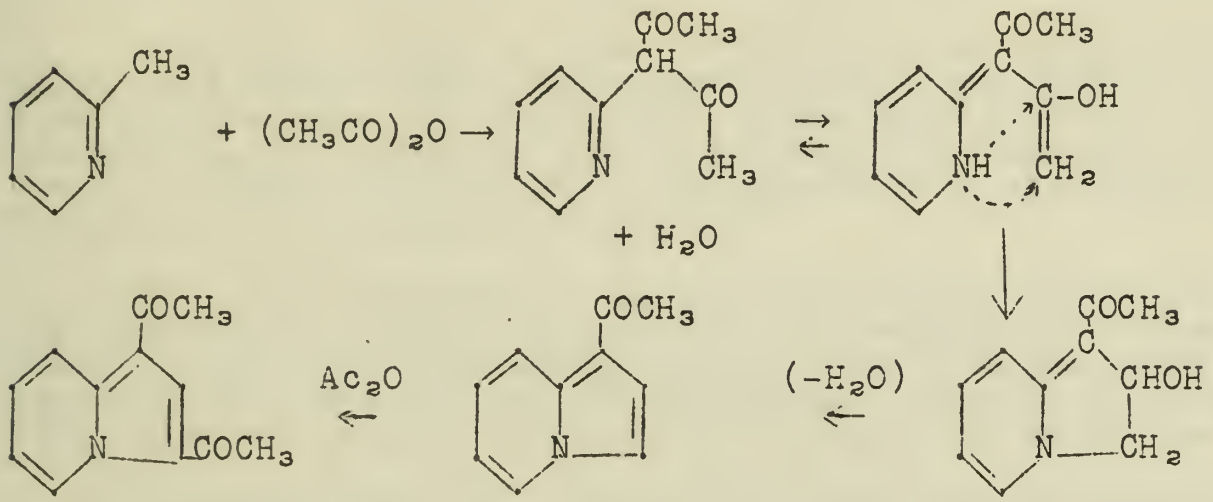


$$+ NaX + 2H_2O + CO_2$$

The reaction proceeds less smoothly with α-halogenated aldehydes. Attempts to prepare pyrrocolines substituted in the 3-position by acetyl, carbethoxy or nitro groups by the use of halogenated β-diketones, acylacetates and acylnitromethanes have been unsuccessful. The reaction appears to be general for pyridines containing a methyl or methylene group in the α-position. The use of quinaldine would be expected to give 5,6-benzopyrrocolines, but results have been unsuccessful.



(2) α-Methylpyridines + Acetic anhydride (6).--This method consists of heating an α-methylpyridine with acetic anhydride at 200-220° in a sealed tube. The 1,3-diacetylpyrrocoline thus obtained can be hydrolyzed to remove the acetyl groups. Formation of the 1,3-diacetylpyrrocoline has been explained as follows.



The reaction has a limited application and only gives yields of 10-25% of the diacetyl compounds. Other anhydrides than acetic have been studied but only in the case of propionic anhydride could a definite product be isolated. This was 1-propionyl-3-methyl-pyrrocoline.

(3) Miscellaneous Methods (7).--Diels and his collaborators found that pyridocoline derivatives obtained by the action of acetylenedicarboxylic esters on pyridine and similar bases could readily be broken down to compounds of the pyrrocoline series. This is not a very good synthetic method since the yields are rather low.

REACTIONS:

The pyrrocolines are solids with weakly basic properties. They fluoresce in dilute solution, are usually fairly stable to air and light, and give a pyrrole reaction with a pine splinter and an indole reaction with oxalic acid. The pyrrocoline ring system contains a pyrrole ring and a dihydropyridine ring. Reactions generally affect the pyrrole ring.

(1) Acetylation (1-3,5,6,8).--Pyrrocoline, and its 2-methyl and 2-phenyl derivatives, upon refluxing with acetic anhydride and sodium acetate give the 3-monoacetyl compounds in 70-90% yields. Treatment of these monoacetyl compounds with acetic anhydride at 220-240° in a sealed tube yields the 1,3-diacetyl compounds.

Attempts to prepare the monoacetyl derivatives from 2-methyl- and 2-phenylpyrrocoline by the Friedel Crafts method with acetyl chloride or bromide were unsuccessful.

Japanese workers readily obtained the 1,3-diacetyl derivative from 3-acetyl-2-methylpyrrocoline with acetyl chloride and aluminum chloride in tetrachloroethane solution but the English workers were unable to repeat this work. However, using the same procedure on 3-acetyl-2-phenylpyrrocoline they obtained an 82% yield of the 1,3-diacetyl derivative. It was impossible to introduce acetyl groups into nitroso and nitro pyrrocoline derivatives.

The acetyl groups in both the mono and the diacetyl derivatives of 2-methyl- and 2-phenylpyrrocoline were shown to be in the five-membered ring by oxidation with hydrogen peroxide. α-Picolinic acid N-oxide is formed together with benzoic acid in the case of 2-phenyl derivatives. The position of the acetyl group was finally established by reduction.

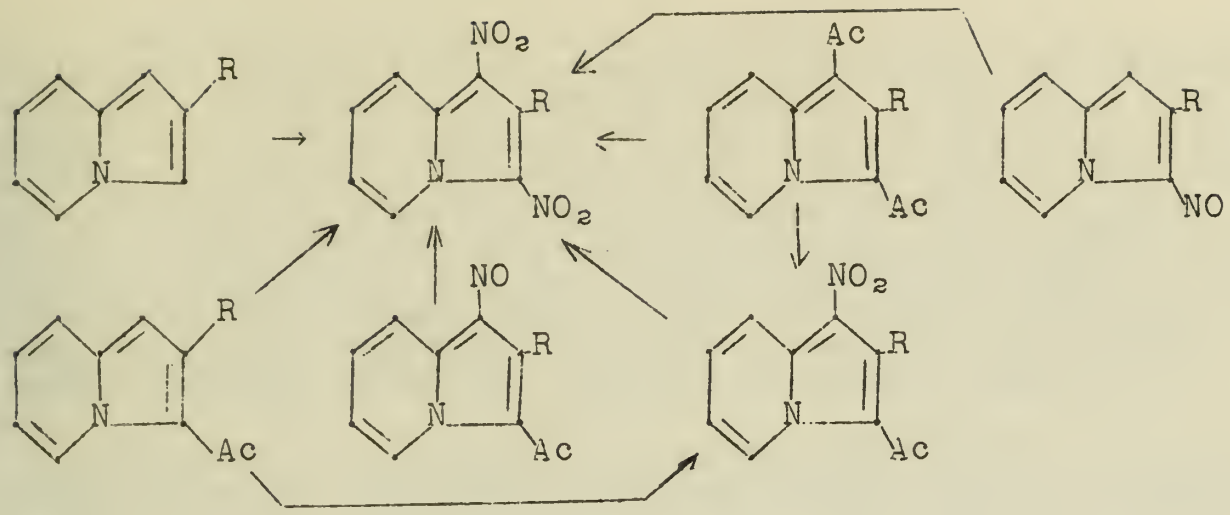
The acetyl compounds of pyrrocoline and its alkyl and aryl derivatives are readily deacetylated by heating with dilute hydrochloric acid, while the acetyl derivatives of nitroso and nitro pyrrocolines are resistant to hydrolysis. Ketonic reagents react with only one carbonyl group of the diacetyl pyrrocolines.

(2) Nitrosation (2).--The pyrrocoline nucleus undergoes nitrosation without difficulty by the action of sodium nitrite in acid solution. Nitrosation of 2-methyl- and 2-phenylpyrrocoline gives 3-nitroso compounds. With the 3-acetyl derivatives of these compounds and 3-ethyl-2-methylpyrrocoline 1-nitroso products result. In all cases 80-90% yields are obtained.

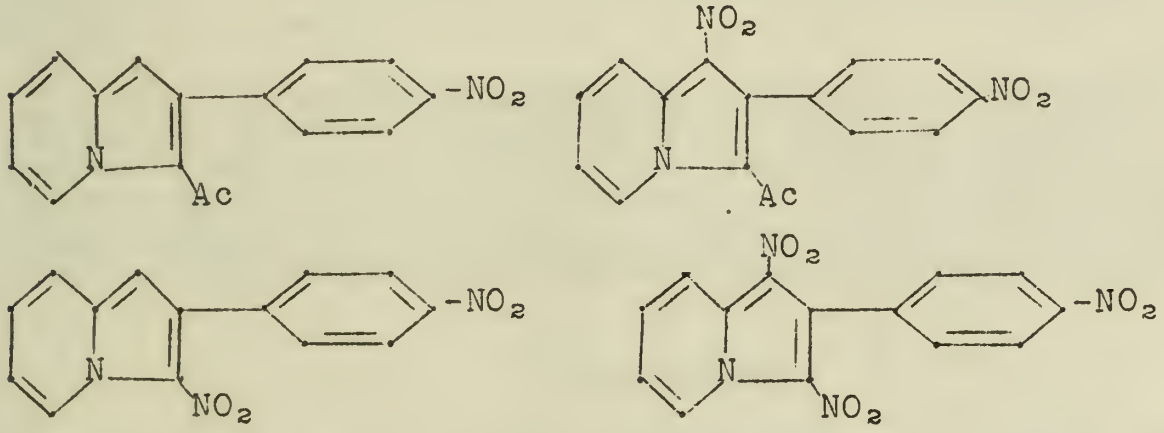
Oxidation of the nitroso compounds with hydrogen peroxide gave α-picolinic acid N-oxide. This indicated that the nitroso groups were contained in the pyrrole ring. The position of the nitroso group in the 2-methyl compound was proved by oxidation to 2-methyl-3-nitropyrrocoline. Proof that the nitroso group was in the 3-position of the 2-phenyl derivative was furnished by direct synthesis from α-picoline and ω-chloroisonitrosoacetophenone.

(3) Nitration (3).--The nitration of 2-methyl-, 2-phenylpyrrocoline and their 3-acetyl and 1,3-diacetyl derivatives has been thoroughly studied.

Nitrations which can be accomplished by the use of nitric acid in acetic acid are shown in the following scheme. Yields were usually good, ranging from 40-90%.



The results obtained with a mixture of nitric and sulfuric acids are different from those of the preceeding method. 2-Methylpyrrocoline yields the 1-mononitro and the 3-mononitro derivatives. 3-Acetyl-2-methylpyrrocoline gives the corresponding 1-nitro compound. Nitration of 2-phenylpyrrocoline with one mole equivalent of nitric acid yields 2-(p-nitrophenyl)pyrrocoline. Use of excess nitric acid gives 1-nitro-2-(p-nitrophenyl)pyrrocoline. Products obtained upon nitration of 3-acetyl-2-phenylpyrrocoline are shown below.



Structures of the nitro compounds were determined by oxidation, further nitration of mononitro derivatives, acetylation, and oxidation of nitroso compounds.

(4) Reduction of 3-Acetyl Derivatives (4).--A modified Clemmensen method afforded reduction of the carbonyl group to give 3-ethyl-2-methylpyrrocoline in small yield. 3-α-Hydroxyethyl-2-methylpyrrocoline was also formed. Reduction of 3-acetyl-2-phenylpyrrocline by the Wolff-Kishner method gave a 35% yield of the 3-ethyl compound although a larger amount of 2-phenylpyrrocoline was also formed during the reaction. The structure of the 3-ethyl derivatives was proven by direct synthesis according to Tschitschibabin's method.

Selective reduction of the carbonyl group by means of catalytic methods without affecting the nucleus was impossible. Reduction of 3-acetyl-2-methylpyrrocoline using Raney nickel catalyst at 150 atmospheres and 180° gave 3-ethyl-2-methyloctahydropyrrocoline in 74% crude yield. With PtO_2 at room temperature and atmospheric pressure three pyrrocolines were obtained, namely, the 3-acetyl-2-methyl-5,6,7,8-tetrahydro-, the 3-α-hydroxyethyl-2-methyloctahydro-, and the 3-ethyl-2-methyloctahydro- derivatives. Yields of these ranged from 15-45%. 2-Methyl-, 3-methyl-, and 2,3-dimethylpyrrocoline have been reduced to the corresponding octahydro compounds with PtO_2 catalyst in 70-80% yields (9).

Reduction of 2-phenylpyrrocolines with Raney nickel at room temperature and atmospheric pressure gives 5,6,7,8-tetrahydro derivatives in excellent yield. With the 3-acetyl compound the carbonyl group was not reduced. Under vigorous conditions, 125 atmospheres and 180°, reduction of 3-acetyl- and 3-ethyl-2-phenylpyrrocoline give 2-cyclohexyl-3-ethyloctahydropyrrocoline in 80-90% yields. Reduction of 3-acetyl-2-phenylpyrrocline using copper chromite catalyst results in the formation of a mixture of 3-ethyl-2-phenyl-5,6,7,8-tetrahydropyrrocoline and the corresponding octahydro compound in yields ranging from 20-50%.

Structures of the catalytic reduction products were based on color tests, reactions with 2,4-dinitrophenylhydrazine and phenylisocyanate, deacetylation and acetylation reactions and ultraviolet absorption studies.

(5) Miscellaneous Reactions.--Reactions of pyrrocolines with aldehydes, ketones, diazonium salts, Grignard reagents, quinone, maleic anhydride, and iodine have been reported in the literature. In most cases tentative structures of the resulting compounds have been assigned based on similar reactions with pyrrole and indole derivatives, but structure proofs have not been carried out.

Bibliography

Borrows, Holland and Kenyon, (1) J. Chem. Soc., 1946, 1069; (2) ibid., 1075; (3) ibid., 1077; (4) ibid., 1083.
(5) Tschitschibabin, Ber., 60, 1607 (1927); (with Stepanow), 62, 1068 (1929); 63, 470 (1930).
(6) Scholtz, Ber., 45, 734 (1912); (with Fraude), ibid., 45, 1718 (1912); ibid., 46, 1069 (1913); Archiv Pharm., 251, 666 (1913).
(7) Diels and Schrum, Ann., 530, 68 (1937) and earlier papers.
(8) Ochiai, J. Pharm. Soc. Japan, 60, 164 (1940); C. A., 34, 5449 (1940).
(9) Ochiai and Tsuda, Ber., 67, 1011 (1934).

Reported by Gerhard W. Leubner
March 28, 1947

MAGNETIC PROPERTIES OF SOME ORGANIC COMPOUNDS

Introduction.--All organic species can be classified into two magnetic groups depending on whether or not they contain unpaired electrons. Those possessing only paired electrons are classed as "diamagnetic", while those containing unpaired electrons in addition to paired electrons are classed as "paramagnetic". Differentiation between these two classes is possible by observing their respective behaviours in a magnetic field. Diamagnetic substances when suitably suspended in an inhomogeneous magnetic field suffer an apparent decrease in weight, while paramagnetic substances apparently increase in weight. As a result of their unpaired electrons paramagnetic molecules possess permanent magnetic dipoles, the magnitudes of which are dependent upon temperature. On the other hand, diamagnetism is practically independent of temperature, and diamagnetic molecules have magnetic dipole moments only in the presence of a magnetic field.

In measuring the magnetic properties of substances, the material in question is usually weighed in the presence of and in the absence of a magnetic field, the difference in weight corresponding to the magnetic susceptibility of the substance (1).

Diamagnetism.--Pascal (1910-1925) (2) carried out extensive investigations of the diamagnetic susceptibilities of a large number of organic compounds and was able to show that the molar susceptibility was expressable as the sum of the atomic susceptibilities if certain corrections were applied for constitutional peculiarities. He assigned values for different types of bonds and showed that the values maintained their identity in a large variety of compounds. Gray and Cruickshank (3) replaced the empirical standards of Pascal by a system which permits the direct determination of constitution on the basis of magnetic measurements. Pascal's methods led to the conclusion that the Kekule benzene formula was incorrect and this new method of calculation made it possible to take hybridizations into account. In this way they were able to reconcile the experimental and the calculated values for the magnetic susceptibility.

Diamagnetic susceptibility has been used by Farqueson (4,5) in following the progress of polymerization, 2,3-dimethylbutadiene in particular. When a substance containing double bonds and the ability to polymerize is subjected to magnetic measurements in the course of polymerization, it is found that the diamagnetic susceptibility changes as polymerization goes on due to the disappearance of a double bond and the formation of a single bond.

Pacault and Buu-Hoi (6,7) have applied magnetic measurements to the investigation of the structures of some polycyclic compounds. The existence of mesomeric forms of polycyclic hydrocarbons has been shown and their proportion determined by comparisons of the magnetic susceptibilities.

Paramagnetism.--Free Radicals.--Compounds such as the hexaaryl ethanes are diamagnetic in the undissociated state. Dis-

sociation leads to the existence of lone electrons which donate paramagnetic properties to the radicals. If the compound is 100% dissociated the paramagnetic susceptibility would be 1260 x 10^{-6} emu. Thus if the experimental susceptibility is known, together with the diamagnetic susceptibility (from Pascal standards), it is possible to calculate the per cent dissociation and the equilibrium constant. The heats of dissociation of the compound can be calculated from the rate of change of the equilibrium constant with temperature (8,9, 10). Similar effects are known in the nitrogen free radicals (11, 12,13).

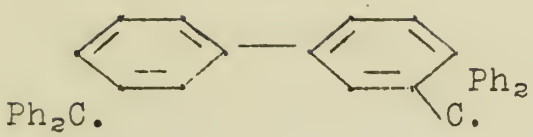
Semiquinones.--Michealis and collaborators (14,15) have investigated the course of slow reduction of quinones with respect to the change of magnetic susceptibility during reduction. It has been demonstrated that reduction of organic compounds takes place in two univalent steps and on the basis of this principle the reduction of quinone (I, diamagnetic) should occur in two steps. The addition of the first electron should result in the formation of a paramagnetic "semiquinone" (II). The addition of the second electron would cause the formation of the divalent anion of hydroquinone (III). This is difficult to show in the case of benzo-

I II III

quinone because of irreversable secondary reactions, but in the case of duroquinone the methyl groups prevent any such reaction and the existence of a semiquinone structure can be shown by magnetic methods.

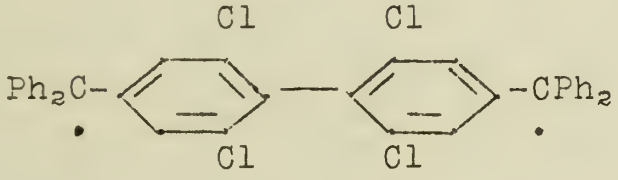
Diradicals.--In the phenyl and biphenyl series, true biradicals exist only where no intramolecular stabilization is possible (o-compounds) or where there is no possibility of a valence tautomeric quinonoid structure. The Tschitschibabin hydrocarbon (16) was one of the first compounds believed to be in the diradical state. Solutions of this compound were, however, found to be

diamagnetic (17). The first compound of this type found to be paramagnetic in solution was the Schlenk hydrocarbon (18,17).



8% dissoc. at 75°C.

The relationship between noncoplanarity and paramagnetism in this series was shown by means of the hindered compound (19).



18% dissoc. at 18°C.

The compounds of the quinodimethane series are all non-paramagnetic (17). A nitrogen diradical arising from porphydrindine is 100% dissociated at room temperature (20). A summary of work in this field is given by Müller (20).

Metal Ketyls.--Müller and Janke (21) have investigated a large number of metal ketyls in an attempt to correlate magnetic behaviour with structure. According to their classification there are three groups of metal ketyls: (A) diamagnetic pinaconates, such as those arising from γ-pyrones, (B) meriradicals of complex structure, such as those derived from xanthone, flavone and chromone, which are more or less paramagnetic, and (C) holoradicals which are strongly paramagnetic and arise from compounds such as benzophenone.

Organic Substances with Elements of the Transitional Group.--This class of compounds includes a large number of biologically important iron-porphyrin compounds such as hemoglobin and the hemochromogens (21). The paramagnetic susceptibility of such complex molecules is largely due to the presence of unpaired electrons on the metal atom bound in the complex. The number of unpaired electrons can be evaluated by a calculation involving the molecular magnetic dipole moment which is accessable through magnetic susceptibility measurements (22).

Bibliography

(1) Michealis, "Physical Methods of Organic Chemistry", Vol. II, Interscience Publ., 1946, p. 1213.
(2) Pascal, Ann. chim. phys., numerous papers, 1910-1925.
(3) Gray and Cruickshank, Trans. Faraday Soc., 31, 1491 (1935).
(4) Farquharson, ibid, 32, 219 (1936).
(5) Farquharson and Ady, Nature, 143, 1067 (1939).
(6) Buu-Hoi and Pacault, J. phys. radium, [8], 6, 33 (1945).
(7) Pacault, Compt. rendu, 219, 158 (1944).

(8) Müller and Müller-Rodloff, Ann., 521, 89 (1936).
(9) Marvel and Roy, J. Am. Chem. Soc., 59, 2622 (1937).
(10) Müller and Kruck, Ber., 71B, 1778 (1938).
(11) Katz, Z. Physik., 87, 238 (1933).
(12) Müller, Müller-Rodloff and Bunge, Ann., 520, 235 (1935).
(13) Müller and Wiesemann, Ber., 69, 2157 (1936).
(14) Michealis, Chem. Rev., 16, 243 (1935).
(15) Michealis, et al., J. Am. Chem. Soc., 60, 1678 (1938).
(16) Tschitschibabin, Ber., 40, 1810 (1907).
(17) Müller and Müller-Rodloff, Ann., 517, 134 (1935).
(18) Schlenk and Brauns, Ber., 48, 723 (1915).
(19) Müller and Neuhoff, ibid, 72, 2063 (1939).
(20) Müller, Z. Elektrochem., 45, 593 (1939).
(21) Müller and Janke, ibid., 45, 380 (1939).
(22) Pauling and Coryell, Proc. Natl. Acad. Sci. US., 22, 210 (1936).
(23) Organic Seminar Abstract, March 21, 1947.

Reported by J. L. R. Williams
April 11, 1947.

THE ALDOL CONDENSATION AND THE CHARACTER OF KETO-PARACONIC ACIDS

The mechanism of the aldol condensation which has been accepted most widely is explained by Hammett as follows:

$$H_3C\text{-}CHO + B \rightleftharpoons [H_2C\text{-}CHO]^- + BH^+ \qquad (I)$$

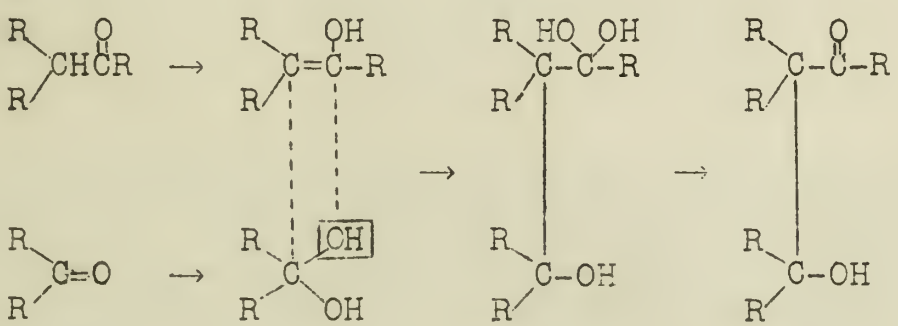
$$[H_2C\text{-}CHO]^- + H_3C\text{-}CHO \rightleftharpoons [H_3C\text{-}\underset{\underset{|O|}{}}{\overset{H}{C}}\text{-}CH_2CHO]^- \qquad (II)$$

$$[H_3C\text{-}\underset{\underset{|O|}{}}{\overset{H}{C}}\text{-}CH_2CHO]^- + BH^+ \rightleftharpoons H_3C\text{-}CHOHCH_2CHO + B \qquad (III)$$

In the first step the aldehyde gives up a proton to the basic catalyst. Then the ionic fragment thus formed adds to the carbonyl group of another aldehyde. This active complex is then stabilized by accepting a proton. All the steps are reversible.

In the reaction of acetaldehyde the rate is first order in aldehyde and nearly proportional to the hydroxy-ion concentration. This is evidence that reaction I is the rate determining step, as is the fact that no deuterium becomes attached to carbon when the reaction is run in heavy water. If the second step were rate determining, the first would be mobile and the pickup of deuterium would be faster than the condensation.

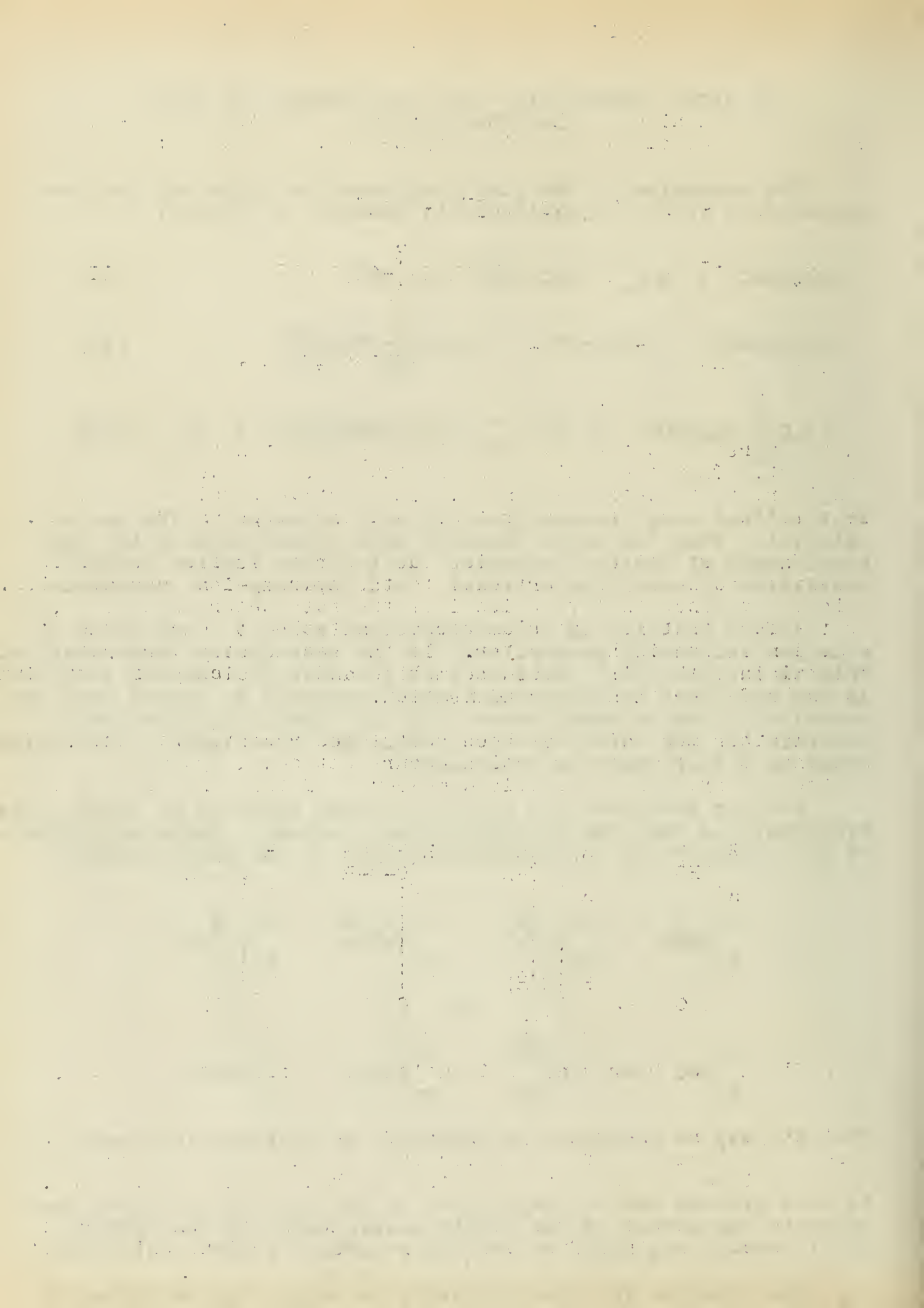
Another mechanism has been postulated recently by Gault. His hypothesis is that the reaction occurs between a hydrated molecule of the aldehyde and an enolized molecule of the same aldehyde.



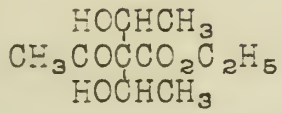
(The R's may be hydrogen, or identical or different radicals).

In this picture one hydroxyl group of the hydrated aldehyde has added to one carbon of the enolic double bond and the hydroxyalkyl residue has added to the other carbon of the double bond.

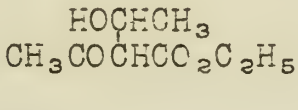
The evidence for this picturing is merely the character of the products obtained from various related reactions which Gault



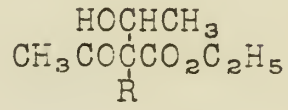
carried out. For example, from the reaction of acetaldehyde with acetoacetic ester there were isolated products of the type I and II.



(I)



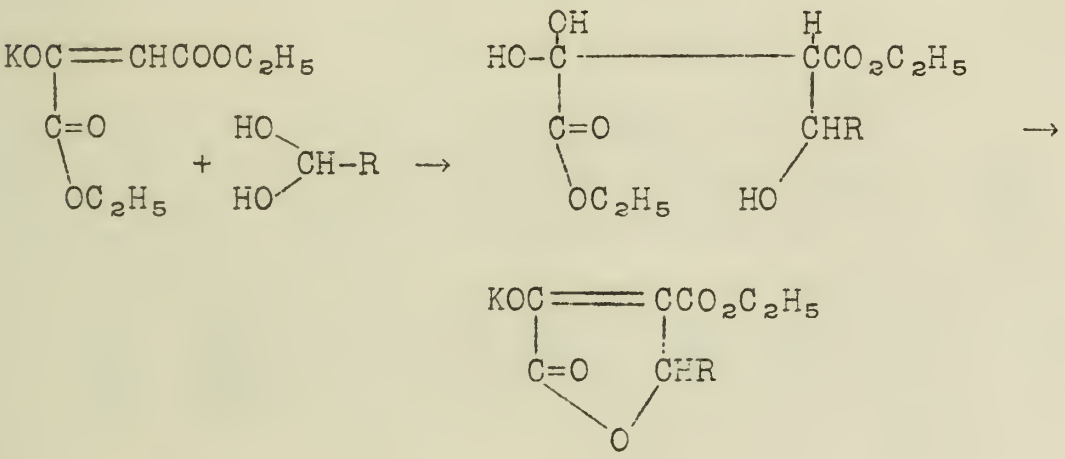
and



(II)

Compounds of this type had not been isolated previously, presumably because they are so reactive in the usual condensation media. Gault postulates their formation as intermediates in all reactions of aldehydes with acetoacetic ester.

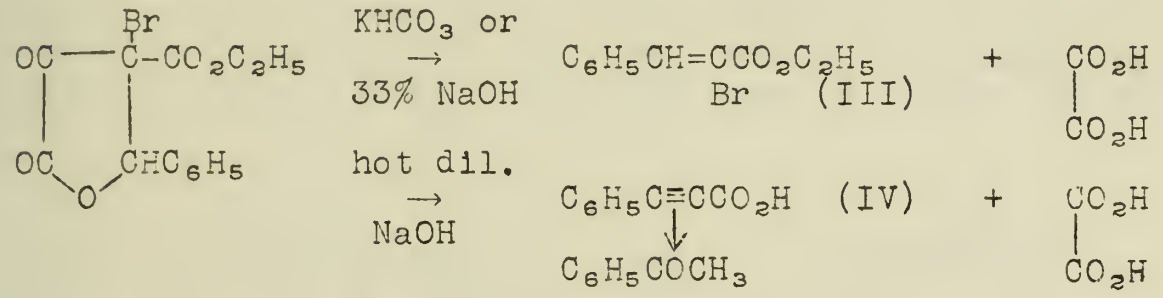
Another reaction studied by Gault and used by him to explain the aldol condensation is that of oxalacetic ester with an aldehyde. If the aldehyde is aromatic, or if the potassium salt of oxalacetic ester is used, the product is cyclic. Gault describes the formation of this compound, a ketoparaconic ester, as follows:



The first compound of this type was reported in 1892 by Wislicenus. It resulted from the reaction of benzaldehyde with oxalacetic ester. Operating with the potassium salt of the ester, Gault prepared other compounds of the series from acetaldehyde, chloral, monochloroacetaldehyde, and 2,3-dibromopropionaldehyde. The ketoparaconic esters give the usual ketone derivatives such as phenylhydrazones, red colorations with ferric chloride, and are usually acidic enough to be titrated with N/2 NaOH. They can be brominated in aqueous solution, the bromine substituting in the lactone ring as evidenced by the fact that the brominated product no longer gives a color with ferric chloride.

Hydrolysis of the phyenylbromoketoparaconic ester with potassium bicarbonate or with cold 33% sodium hydroxide yields

equimolar quantities of oxalic acid and α-bromoethylcinnamate(III). Hydrolysis by means of hot 10% sodium hydroxide yields phenylpropiolic acid (IV) (90%), oxalic acid, and acetophenone. Stronger hot alkali yields only phenylpropiolic acid and oxalic acid.



Gault proposed this reaction as a means of going from an aldehyde to the corresponding methyl ketone, but it seems probable that the acetophenone is merely a by-product.

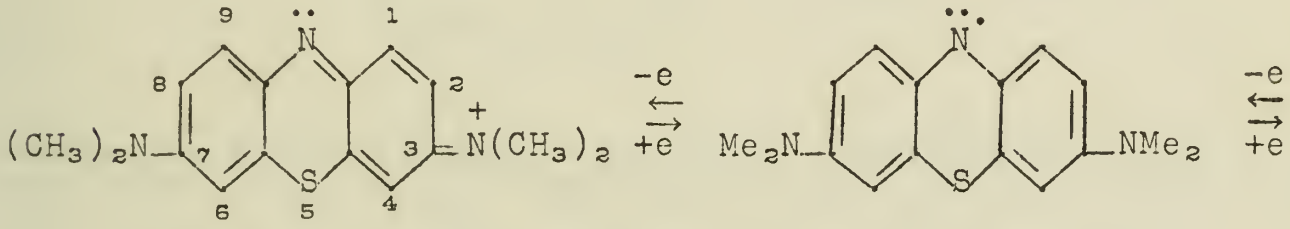
Bibliography

1. Arndt and Eistert, Ber., 69B, 2381 (1936).
2. Bell, J. Chem. Soc., 1937, 1637.
3. Bonhoeffer and Walters, Z. physik. Chem., A181, 441 (1938).
4. Hammett, "Physical Organic Chemistry", p. 343, McGraw-Hill, New York (1940).
5. Gault et al, Bull. Soc. Chem., 3, 549 (1936); (6) Compt. rend., 216, 848 (1943); (7) ibid., 222, 86, 185 (1946); (8) ibid., 222, 294 (1946); (9) ibid., 222, 396 (1946); (10) ibid., 222, 449 (1946).

Reported by T. M. Vial
April 11, 1947

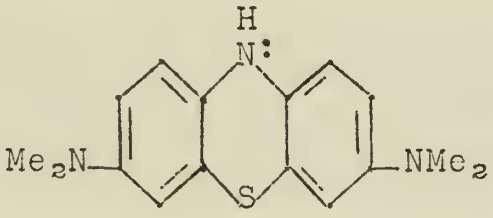
CHEMISTRY OF THE PHENOTHIAZINES

The phenothiazines have recently been investigated for their insecticidal activity, phenothiazine showing a broad spectrum of activity which has led to its wide-spread use against internal parasites(1).Other publications report tests of phenothiazines as potential antimalarials (2) and trypanosomecides (3). The effect of dyes such as methylene blue, related to the oxidized form of phenothiazine, in increasing the rate of respiration of certain cells has been studied (4). This effect is thought to depend on the reversible reduction of such dyes by single electron steps.



Methylene Blue

Methylene Blue Semiquinone



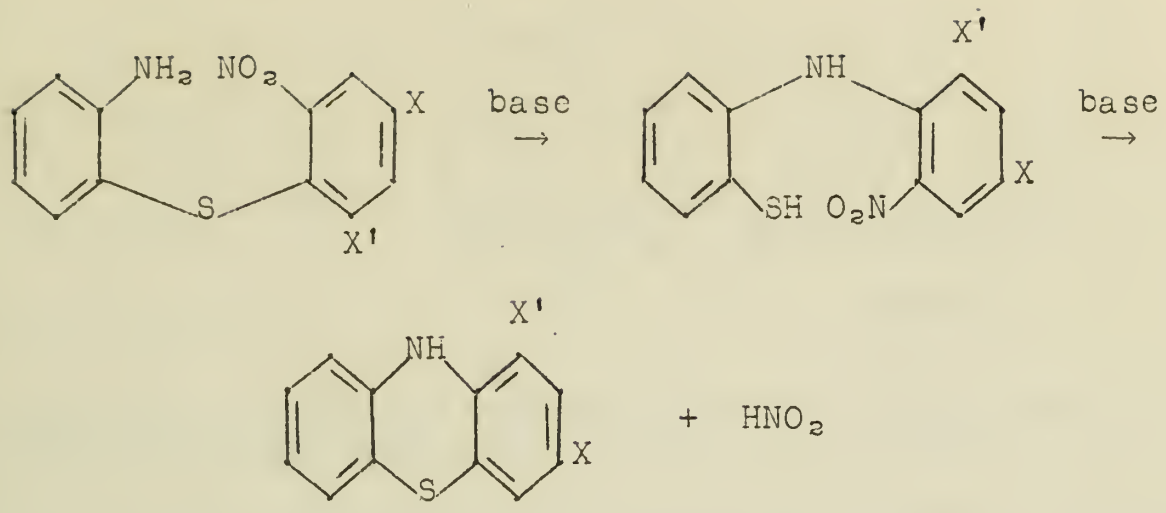
Methylene Blue Leuco Base

METHODS OF PREPARATION.

1. Sulfur fusion.--Phenothiazine is made by fusion of diphenylamine with sulfur in the presence of I_2, $AlCl_3$, or other catalyst, at a temperature where the evolution of hydrogen sulfide becomes rapid, usually about 180-220°. Good yields have been reported for di-β-naphthylamine, and for diphenylamines substituted in the para position by such groups as OH, OMe (5), NH_2, and OCH_2CCOH.(3) Ring deactivating groups prevent reaction.

2. Sulfur dichloride.--An analogous procedure found in the literature involves the treatment of diphenylamines with sulfur dichloride. This has been applied to alkyl-substituted diarylamines, yielding mixtures from which phenothiazines could be isolated in many instances.

3. Rearrangement of diaryl sulfides.--The rearrangement of certain 2-nitro 2'-amino diphenyl sulfides (7) has been shown to proceed to the phenothiazines. The rearrangement is run in aqueous or alcoholic alkali, which may be weaker as the electron-



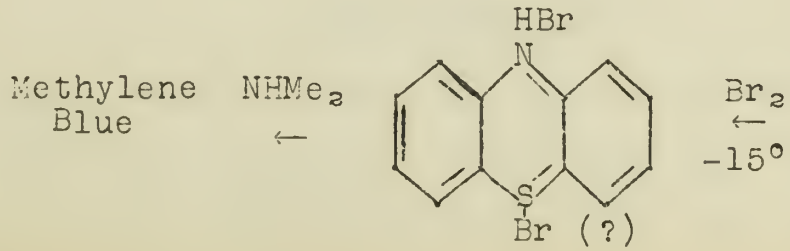
attracting power of X and X' increase. Practically, X and X' are NO_2, COOH, SO_3H, or $\overset{O}{\overset{\|}{C}}-R$. The ring-closure occurs in alkali, but the factors influencing reactivity have not been explored.

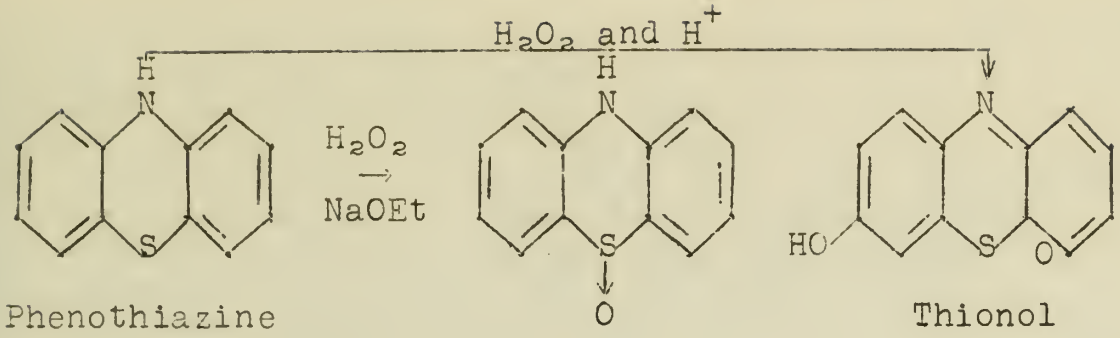
REACTIONS OF PHENOTHIAZINES.

Monosubstitution by the usual reagents into the aromatic rings requires carefully controlled conditions, because of the activitation of the rings and the ease of oxidation of the sulfur. Nitration, for example, gives a mixture of four nitration products, while the sulfur is simultaneously oxidized to sulfoxide.

Many other oxidizing agents, such as hydrogen peroxide, attack the sulfur, especially in slightly alkaline solution, yielding the sulfoxide or sulfone. In acid solution, the three position may be attacked, and thionol produced (9). The sulfoxides may be rearranged to ring-substituted phenothiazines by acids (10,11), hydrochloric acid, for example, yielding a mixture of 3-chloro and 3,7-dichlorophenothiazine. The sulfones are stable to acid.

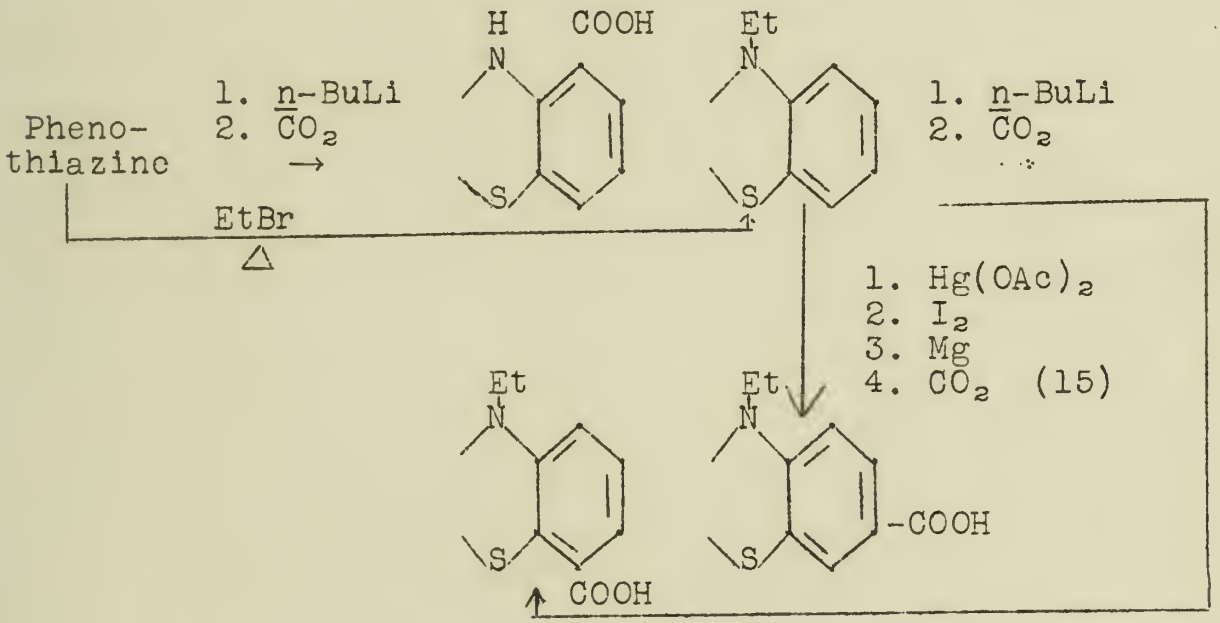
Halogenation of phenothiazine at -15° results in a dibromo compound, often formulated as 5,10-dibromophenothiazine. This is unstable even at 0°, forming nuclear bromination products (12). Should the original dibromo compound be reacted with an excess of ammonia or an amine, 3-amino, or 3,7-diaminothiazine dyes are produced (13).





The amine hydrogen of phenothiazine may be alkylated or acylated in the usual way.

Metalation with n-butyl lithium of phenothiazine followed by carbonation gives phenothiazine-1-carboxylic acid, the nitrogen apparently directing substitution (5). When the nitrogen is alkylated or arylated before metalation, however, the 4-carboxylic acid forms, the sulfur directing to the more usual ortho position.



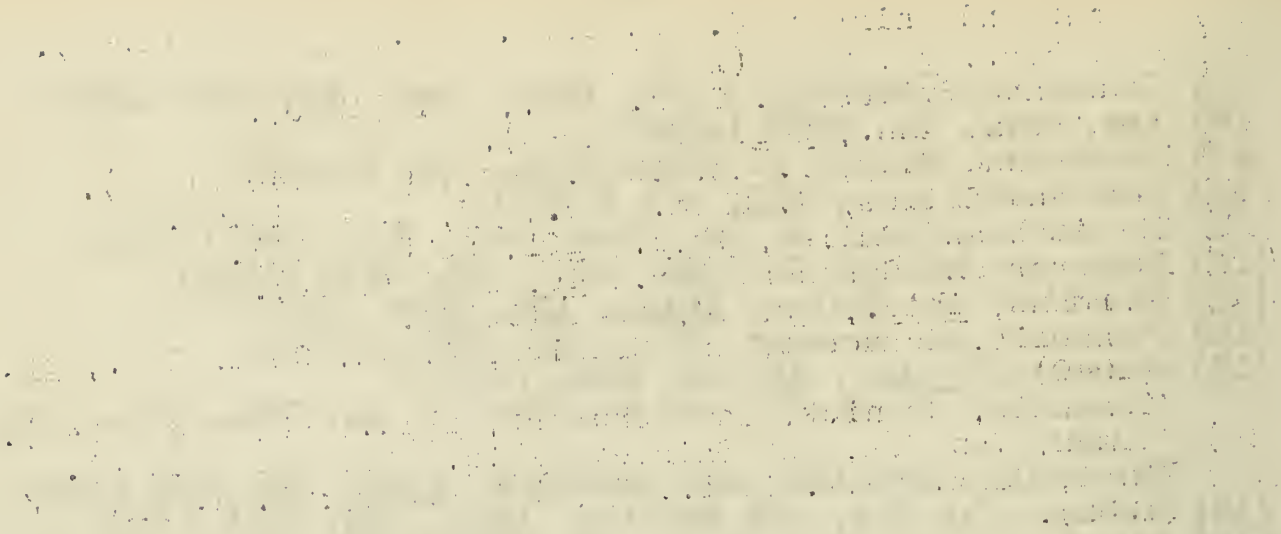
The Friedel-Crafts reaction may be run, preferably on 10-acylated phenothiazine, to give 2-substituted products. The 2-acetyl compound, prepared by using acetyl chloride, is oxidized to phenothiazine-2-carboxylic acid by hypochlorite.(3).

Bibliography

(1) cf. Benham, Can. J. Research, 23E, 80 (1945) in C. A., 39, 4688 (1945).
(2) Bernstein and Rothstein, J. Am. Chem. Soc., 66, 1886 (1944).
(3) Baltzly et al, ibid., 68, 2677 (1946),
(4) Granick, Michaelis and Schubert, ibid., 62, 204 (1940); Michaelis and Smythe, Ann. Rev. Biochem., 7, 4, 18 (1938).

(5) Gilman and Shirley, J. Am. Chem. Soc., 66, 888 (1944).
(6) Kym, Ber., 21, 2807 (1888).
(7) Evans and Smiles, J. Chem. Soc., 181 (1935).
(8) Bernthsen, Ann., 230, 101 (1885).
(9) De Eds and Eddy, J. Am. Chem. Soc., 60, 1146 (1938).
(10) Page and Smiles, J. Chem. Soc., 97, 1115 (1910).
(11) Hilditch and Smiles, ibid., 101, 2295 (1912).
(12) Pummerer and Gassner, Ber., 46, 2310 (1913).
(13) Kehrmann, ibid., 49, 53, 2831 (1916).
Michaelis, Schubert, and Granick, J. Am. Chem. Soc., 62, 1810 (1940)
Michaelis, Granick, and Schubert, ibid., 63, 353 (1941).
(14) Gilman, Van Ess, and Shirley, ibid., 66, 1215 (1944).
(15) Finzi, Gazz. chim. ital., 62, 175 (1932); C. A. 26, 4338 (1932).

Reported by Morton Harfenist
April 11, 1947



LAVANDULOL, A NEW MONOTERPENIC ALCOHOL

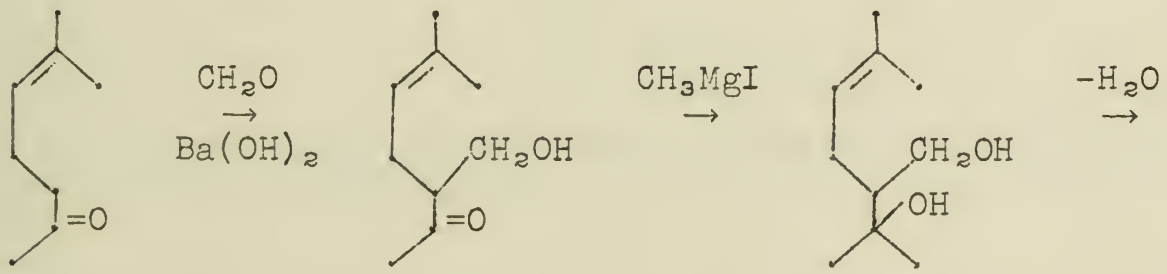
Lavandulol is a monoterpenic alcohol recently isolated from Lavandula vera by Schinz and coworkers (1,2). It has also been found in lavandin (3).

Isolation (1,2).--l-Lavandulol constitutes less than one per cent of French lavender oil, being present in free and esterified form. Isolation from the free alcohol fraction is unsatisfactory, due to the difficulty of complete separation from d-borneol.

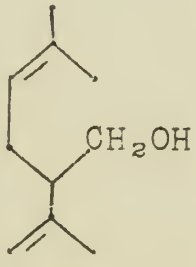
To recover lavandulol from the ester fraction, lavender oil was treated to remove acids and phenols, aldehydes and ketones, and free alcohols, and the residual ester-containing neutral fraction was saponified. The alcohols formed were removed as phthalates, then regenerated and fractionally distilled. The lavandulol-containing fraction was purified by repeated conversions to the allophanate.

Properties (1,4).--Lavandulol is a primary, doubly-unsaturated optically-active monoterpenic alcohol, resembling geraniol in odor and in melting points of derivatives. It is more stable than geraniol, from which it differs in its failure to react with calcium chloride or to be destroyed by phthalic anhydride at 200°. On hydrogenation, exactly two moles of hydrogen are taken up. The boiling point is about 15° lower than that of geraniol, indicating a greater degree of branching in the carbon chain.

Synthesis (1,5).--A more highly-branched alcohol (IV), whose properties agreed well with those of lavandulol, had been prepared by Ruzicka and Roethlisberger (5) as follows.



I II III

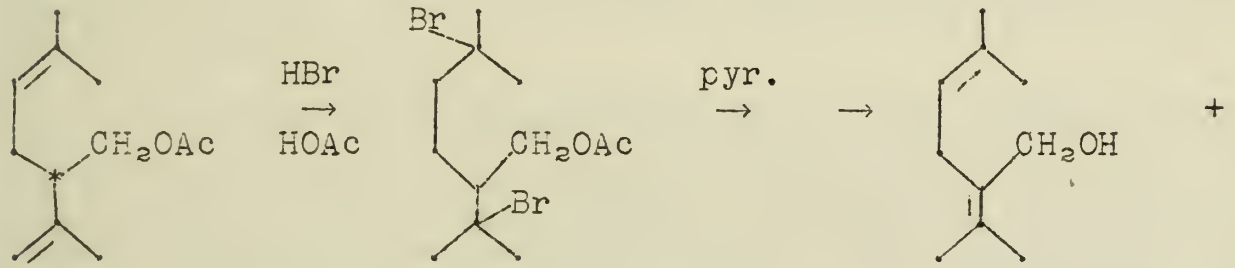


IV

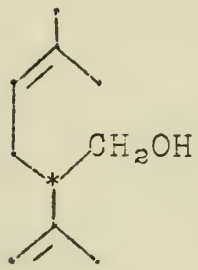
Dehydration of III has been shown to give IV rather than the α,β-unsaturated compound (6).

Proof of Identity (4).--Conclusive proof of the identity of lavandulol with IV was obtained by comparing related products in which the asymmetric center had been destroyed.

Lavandulol was isomerized to isolavandulol (VII) by dehydrohalogenation of the dibromide. Assuming the structure IV for lavandulol, the reaction may be formulated:

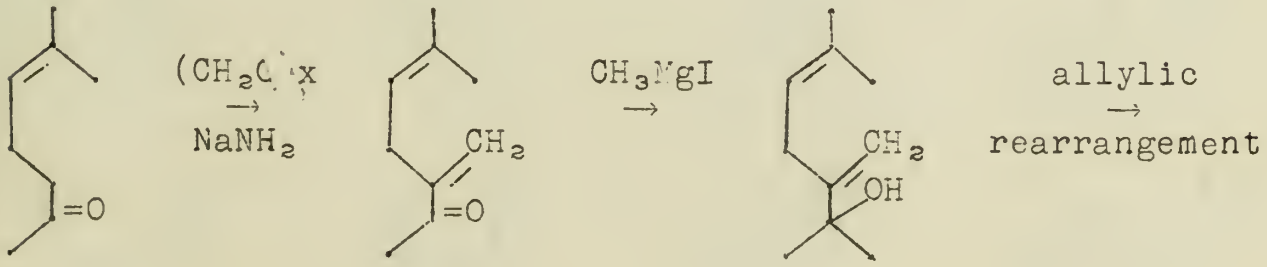


V VI VII (2/3)

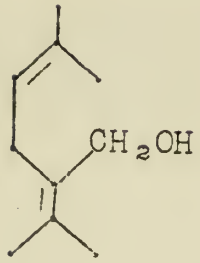


IV (1/3)

2,6-Dimethyl-5-hydroxymethylheptadiene-2,5 (X) was prepared synthetically as follows.



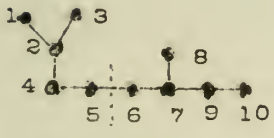
I VIII



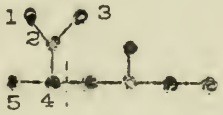
X

The compounds VII and X were compared and found to be identical in all their properties, thus establishing the identity of lavandulol as IV.

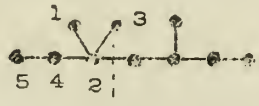
Relationship to the Isoprene Rule.--The isoprene rule was first stated by Wallach (7), who suggested in 1887 that isoprene is the fundamental building unit of the terpenes and polyterpenes. Most naturally occurring terpenes are composed of isoprene units joined in head-to-tail fashion (A-I). Nine "irregular" arrangements are also theoretically possible, as classified by Schinz (4,8).



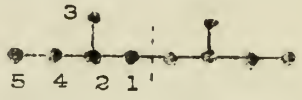
A-I (p-cymene)



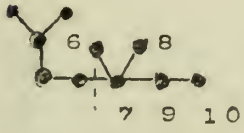
B-I (m-cymene)



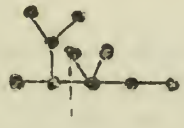
C-I



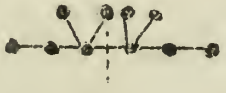
D-I



A-II

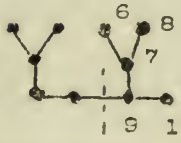


B-II



C-II

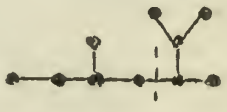
D-II (=C-I)



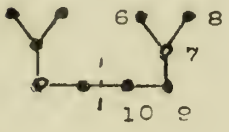
A-III(p-cymene)

B-III

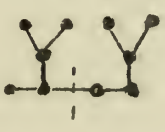
C-III(=B-II)



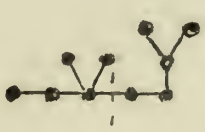
D-III(=B-I)



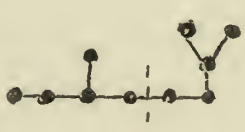
A-IV(m-cymene)



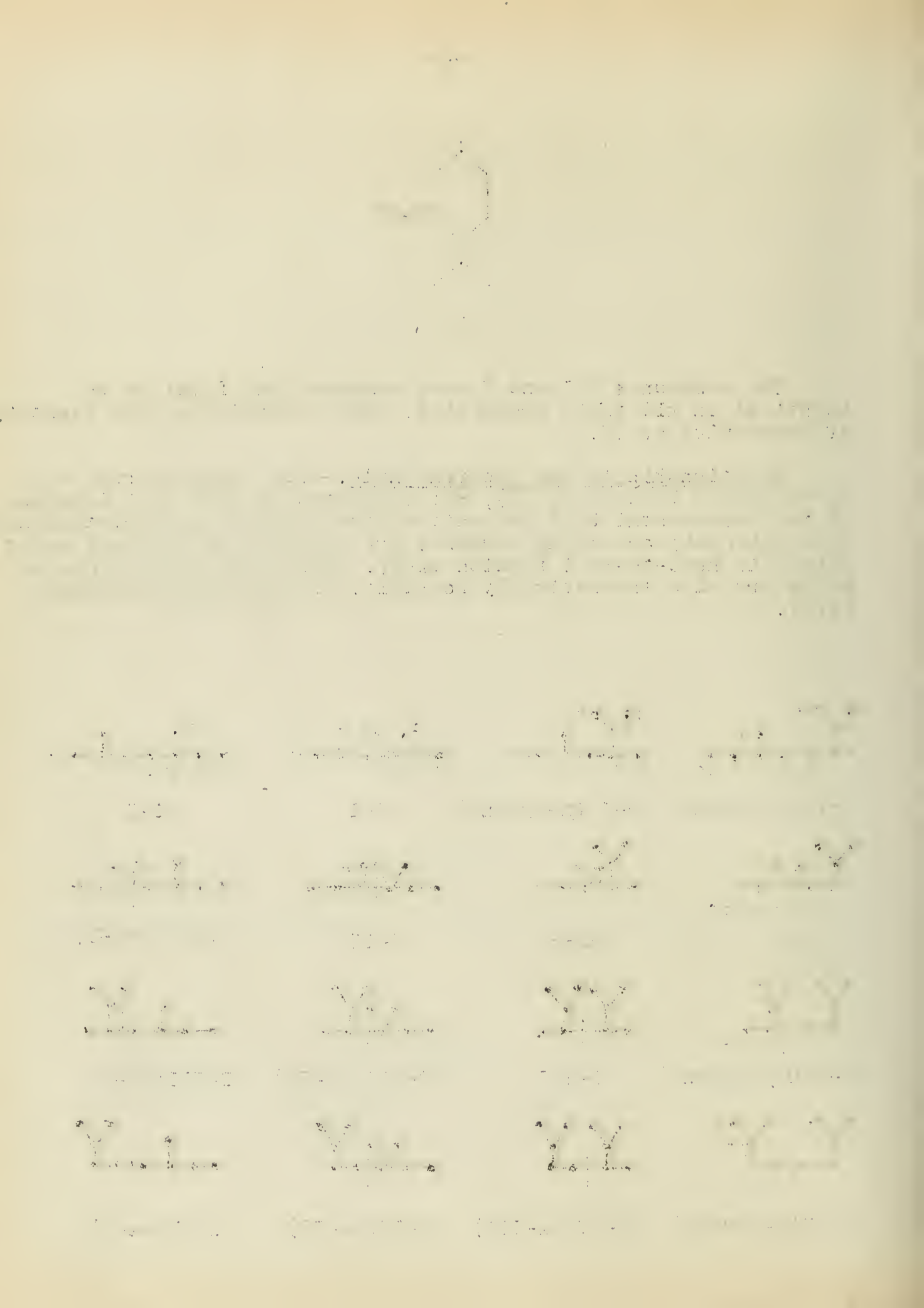
B-IV(=A-III)



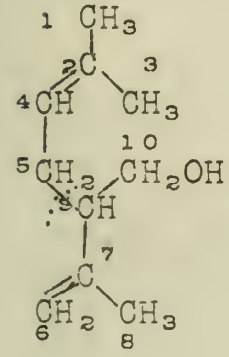
C-IV(=A-II)



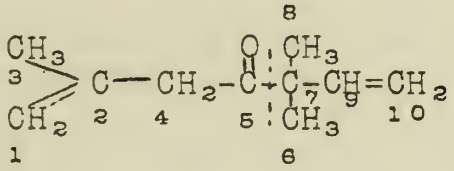
D-IV(=A-I)



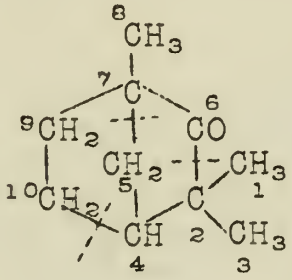
The only known naturally occurring monoterpenes not joined in this fashion (A-I) are lavandulol (IV - class A-III), artemesia ketone (XI - class A-II), and the bicyclic fenchone (XII). The latter may be placed in classes A-II, A-III, or C-I, according to which bonds are broken.



IV



XI



XII

Lavandulol is of further interest as a representative of the only irregular group which is related to p-cymene (4). Further work has been done in synthesizing other terpene-like compounds of irregular structure, including several related to m-cymene (8,9). Study of the properties of these compounds is expected to facilitate the search for other irregular terpenes which may exist in natural products.

Bibliography

(1) Schinz and Seidel, Helv. Chim. Acta., 25, 1572 (1942).
(2) Seidel, Schinz, and Müller, Helv. Chim. Acta., 27, 664 (1944).
(3) Naves, Helv. Chim. Acta., 28, 1220 (1945).
(4) Schinz and Bourquin, Helv. Chim. Acta., 25, 1591 (1942).
(5) Ruzicka and Roethlisberger, Helv. Chim. Acta., 18, 439 (1935).
(6) Pfau and Plattner, Helv. Chim. Acta., 15, 1250 (1932).
(7) Wallach, Ann., 238, 78 (1887); 239, 46 (1887).
(8) Schinz and Simon, Helv. Chim. Acta., 28, 774 (1945).
(9) Schinz and Müller, Helv. Chim. Acta., 27, 57 (1944).

Reported by Ruth C. Pierle
April 18, 1947.

N-BROMO COMPOUNDS IN BROMINATION

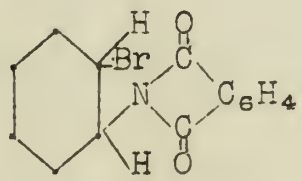
In spite of the importance of bromine-containing compounds in organic synthesis, only a few general methods are ordinarily used in their preparation. The use of free bromine, HBr, PBr_3, and PBr_5 are the ones most commonly known. Another general class of brominating agents which have been extensively examined are those of the N-bromo type.

Quinoline and Pyridine.--When bromine is dissolved in pyridine (or quinoline) plus HBr a compound $C_5H_5NBr_2 \cdot HBr$ is formed in which the bromine is present in the form of a loose molecular compound. The salt can be isolated, but usually the solution is used directly for bromination. This bromination occurs at low energy levels and under very mild conditions, but the reaction is still that of free bromine. This method has been used for mono- and di-bromination of phenols and aromatic amines, and also for the preparation of organometallics such as tri-aryl stannic bromide from tetra-aryl tin.[1,2,3]

N-Bromo-amides, imides, sulfonamides.--Compounds of this type give up their halogen easily and have been used for this reason. Wohl[4] used N-bromo-acetamide to convert phenol and anisole to their p-bromo-derivatives. Also he established the fact that in tetra-methyl- or tri-methyl-ethylene, N-bromo-acetamide substituted a hydrogen in one of the methyl groups to give a compound $(CH_3)_2C=C(CH_2Br)(CH_3)$. However, the yield was low since there was much polymerization. Steinkopf[5] reported the successful halogenation of thiophene with N-chloro and N-bromo acetamide. Also recently Woodward[6] has obtained a dibromo derivative of α-estradiol by the same means. But the difficulty of preparing N-bromo-acetamide limits its use.

Ziegler and coworkers[7] in order to determine if the hydrogen on a carbon adjacent to an olefinic linkage could be replaced investigated other bromoamides. Using first N-bromo-phthalimide and cyclohexene as the olefin, he obtained a 50% yield of the substitution product (I) and 20% of the addition product (II).

I

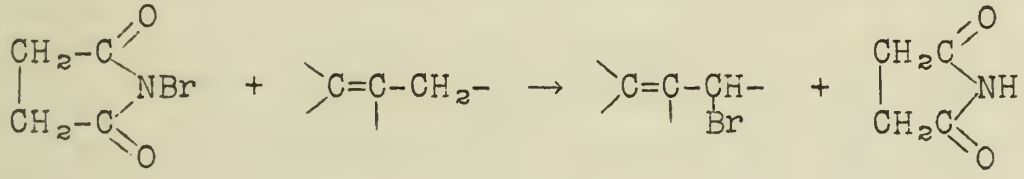


II

Other imides and sulfonamides resulted only in the formation of addition products plus varying amounts of the desired compound. Then N-bromo-succinimide was tried and gave exclusively allyl substitution. Similar imides of glutaric, adipic, and hexahydro-

phthalic acid gave the usual mixture. Also the N-chloroimide released its halogen only under very drastic conditions. The N-bromo-succinimide is easily made, contains 46% bromine and gives only substitution products. The course of the bromination reaction can be followed, for the bromimide is soluble in the CCl_4 solvent, while the resulting succinimide is not.

N-Bromo-Succinimide[7-17].--The general equation for the reaction is as follows.



These substitutions are effected through the simple heating of the two compounds in CCl_4 as a solvent. Reactive solvents cannot be used, nor can compounds be brominated which contain a free $-NH_2$, -OH, or -COOH group, for then HOBr is formed followed by addition to the olefinic bond. All olefins except propylene are readily brominated in the allyl position. Methylene groups are brominated in preference to methyl groups. Also multiple brominations of mono-olefins can be accomplished either through the use of two moles of bromimide or by further bromination of the purified mono-bromide. Methyl or methylene groups next to conjugated double bonds are not brominated nor are tertiary hydrogens replaced by Ziegler's procedure. Karrer and Schmidt[14] however found that both of these brominations would occur if the reaction were catalyzed by benzoyl peroxide. Meystre[11] found in certain cases that ultra-violet light would also catalyze the reaction.

Besides strictly allyl bromination, other highly activated hydrogen atoms can be replaced. Those activated by carbonyl groups or by aromatic -OH or $-NR_2$ groups are brominated readily. For instance, phenolic ethers and acetates, and also dimethyl aniline are brominated in the p-position. Side chains of aromatic hydrocarbons such as in β-methyl naphthalene, and p-nitrotoluene are brominated, as well as side chains of heterocyclics such as α-picoline, 2-methyl thiophene and 2-methyl furan. With peroxides even toluene is converted to benzyl bromide.

Buu-Hoi[10,16] also showed that aromatic hydrogen can be replaced by bromine, if the hydrogen is mobile enough. In this manner 9-bromophenanthrene, 9-bromoanthracene, α-bromonaphthalene, 2-bromothiophene, and 5-bromoacenaphthene among others have been prepared. Benzene itself is not brominated.

The mechanism of the reaction appears to involve free radicals, but no actual mechanism has been presented at this time.

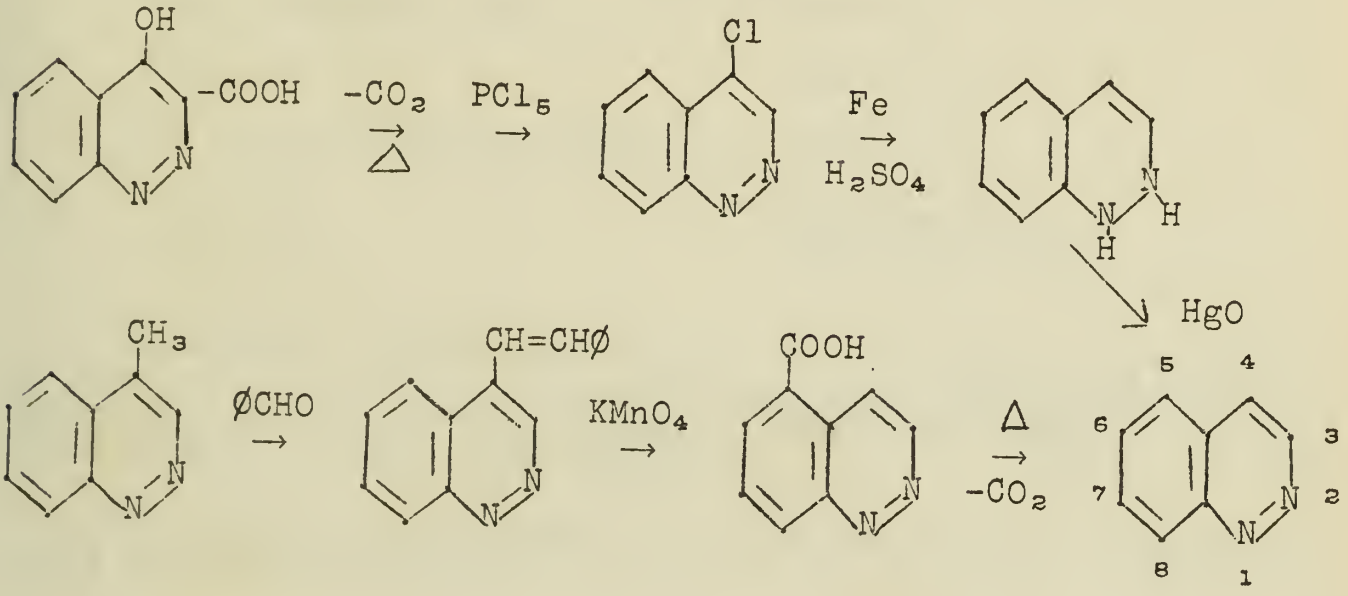
Bibliography

1. Krause and coworkers, Ber., 51, 912 (1918); 52, 2169 (1919); 53, 176, 182 (1920); 54, 2061 (1921); 55, 896 (1922); 56, 1801, (1923).
2. Cross and Cohen, Proc. Chem. Soc., 24, 15 (1908).
3. Trowbridge, J. A. C. S., 21, 68 (1899); 19, 569 (1897).
4. Wohl, Ber., 52, 51 (1919); 54, 476 (1921); 74, 1243 (1941).
5. Steinkopf, Ann., 424, 61 (1921).
6. Woodward, J. A. C. S., 62, 1625 (1940).
7. Ziegler, Spoth, Schaaf, Schumann, Winkelman, Ann., 551, 80 (1942).
8. British Annual Reports, 104 (1943).
9. Ruzicka, Jeger, Redel, Helv. Chim. Acta, 26, 1235 (1943).
10. Buu-Hoi, Ann., 556, 1 (1944).
11. Meystre and coworkers, Helv. Chim. Acta, 27, 1815 (1944); 28, 1252 (1945).
12. Karrer and Rutschmann, Helv. Chim. Acta, 28, 793 (1945).
13. Ruzicka, Plattner and Pataki, Helv. Chim. Acta., 28,1360 (1945).
14. Schmidt and Karrer, Helv. Chim. Acta, 29, 573 (1946).
15. Schmidt, Helv. Chim. Acta, 29, 1144 (1946).
16. Buu-Hoi and Lecocq, J. C. S., 830 (1946); Compt. rend., 222, 1441 (1946).
17. Buu-Hoi, Experimentia, 2, 310 (1947).

Reported by G. L. Shoemaker
April 18, 1947

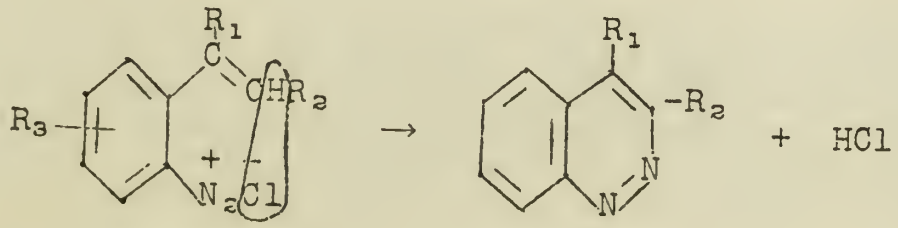
THE CHEMISTRY OF THE CINNOLINES

The cinnolines are derivatives of a binuclear heterocyclic base containing two vicinal nitrogen atoms. The parent compound (I) has been prepared by two methods.

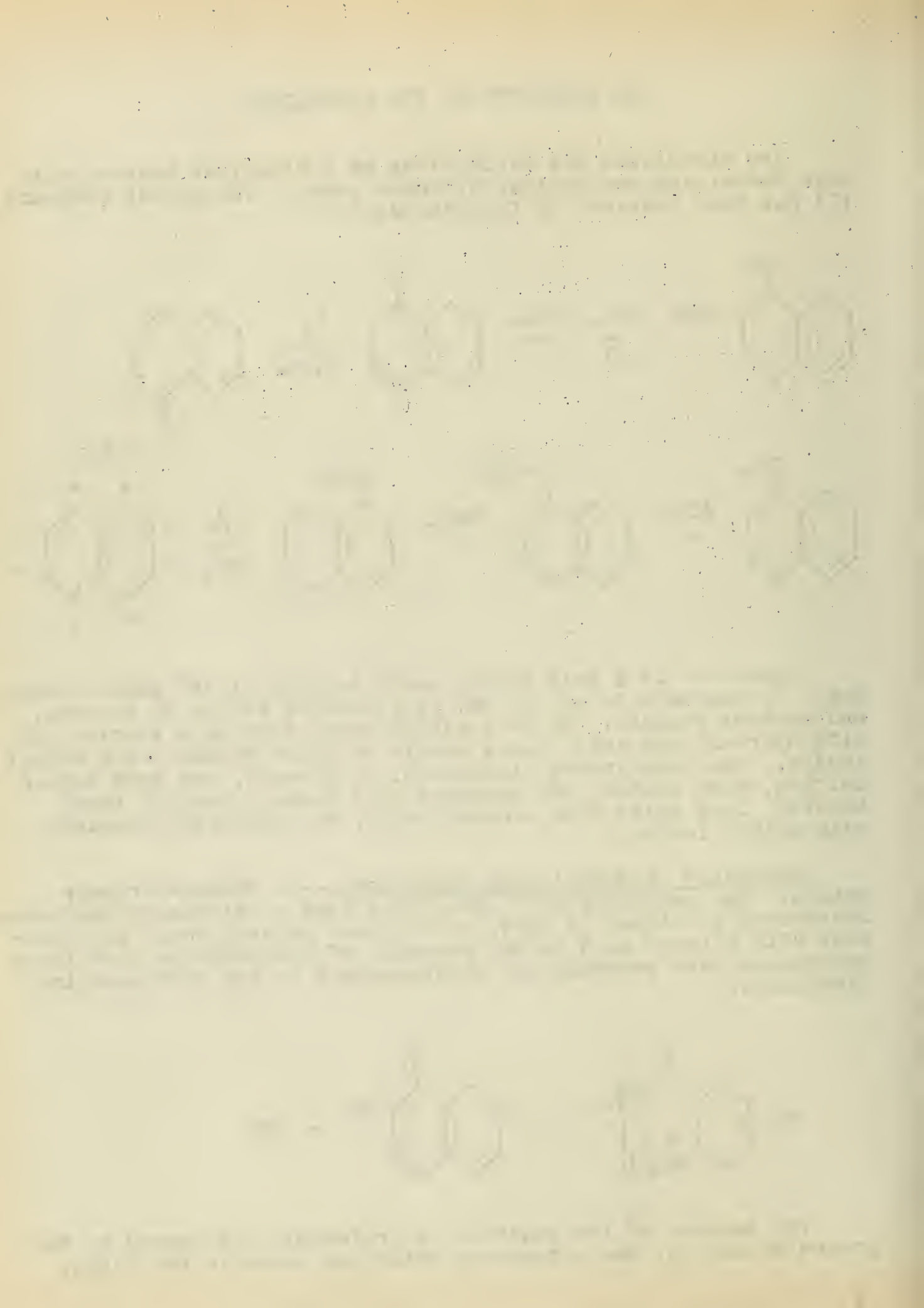


Cinnoline is a pale yellow solid melting at 39° under nitrogen. On exposure to air at 25° it liquefies within 30 seconds, and darkens rapidly. It is a strong base, forming a stable salt with hydrochloric acid, and a stable addition product with methyl iodide. The substituted cinnolines, in general, are much higher melting, more stable, and somewhat less basic. Many of them, however, form salts with mineral acids, and addition compounds with methyl iodide.

Synthesis of Substituted Cinnolines.--1. Widman-Stroemer Method: The preparation of cinnolines from o-aminophenylethylenes, discovered by Widman in 1884, is the most general one. On treatment with nitrous acid in the presence of hydrochloric acid these substances pass smoothly and spontaneously to the corresponding cinnolines.



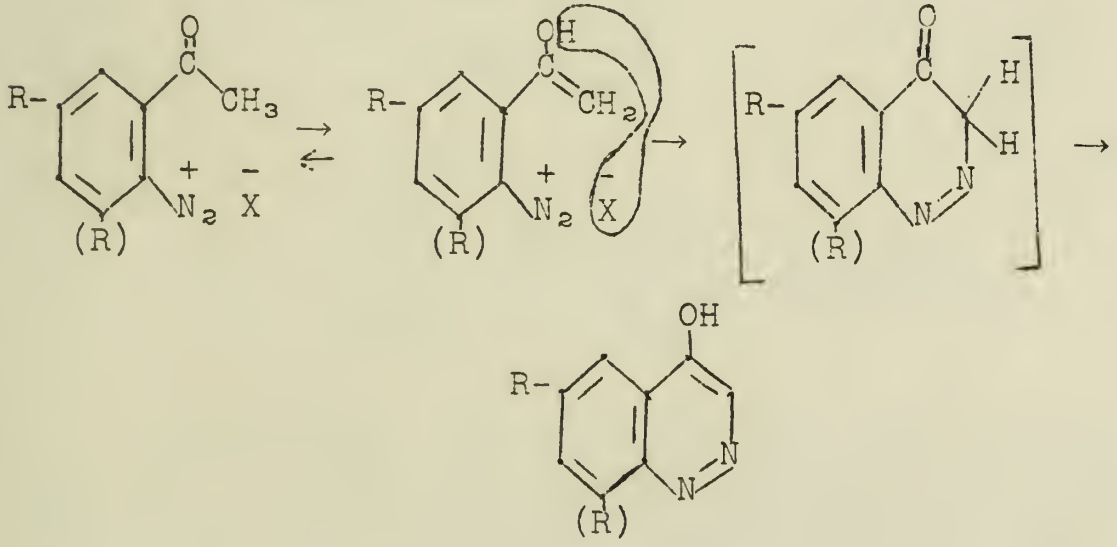
The success of the reaction is profoundly influenced by the groups R_1 and R_2, the effects of which are shown in the table.



R_1	R_2	Result
H	CO_2H, CO_2Et, CN, Ø α-pyridyl, α-quinolyl	No cinnoline
CO_2H	phenyl, m-tolyl	Pschorr
CH_3	H	Cinnoline
Ø	H, CH_3, Ø, $ØCH_2$, α-naphthyl	Cinnoline
	Br	4-Ø-cinnoline with loss of Br

In summary: Cinnolines are not formed when R_1 is either H or COOH, and R_2 is aryl or another negative group; when R_1 is alkyl or aryl (either cis or trans isomer) the tendency to form cinnolines is greatly increased.

2. o-Aminoacetophenones, by a similar process, frequently yield 4-hydroxy cinnolines.

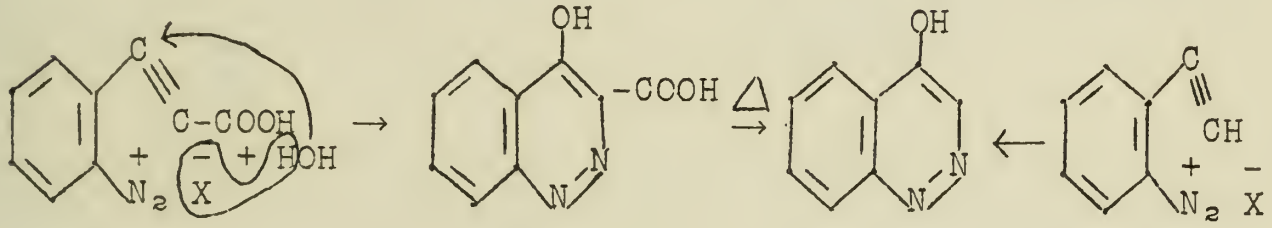


The reaction gives fair yields of the cinnolines (70-90%) when R is Cl, Br, CN, and NO_2. By using the proper starting materials, 3-substituted-4-hydroxy cinnolines can be made. o,ω, and 2,3-diaminoacetophenone, and 6-aminoveratrone failed to yield cinnolines. o-Aminoacetophenone is a borderline case, giving about 10% of 4-hydroxycinnoline, and a large amount of phenolic oil.

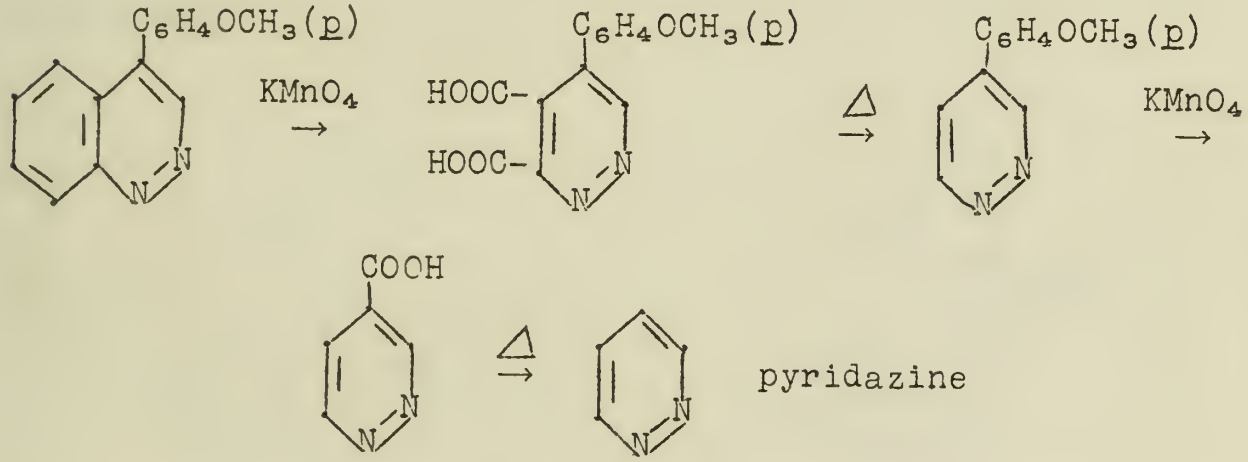
Two factors are important to the success of the reaction. First, and the more important, is the reduction in strength of the ketonic base resulting when electron attracting substituents are present in the 3 and 5 positions (o and p to the amino group). Second, is the ease with which enolization of the ketonic side chain occurs. In the cases mentioned this factor does not seem

to be of primary importance. The effects of 4-substituents have not been determined.

3. Richter Reaction: Cinnolines may be prepared from o-aminophenylpropiolic acids. This method, discovered in 1883, is an old one, but is rarely used because of the difficulty in preparing the starting compounds.



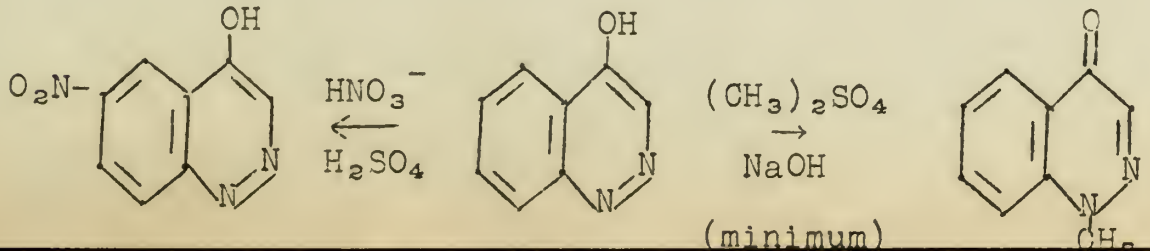
Reaction of Cinnolines.--1. Oxidation: The nitrogen containing ring is stable to oxidation.

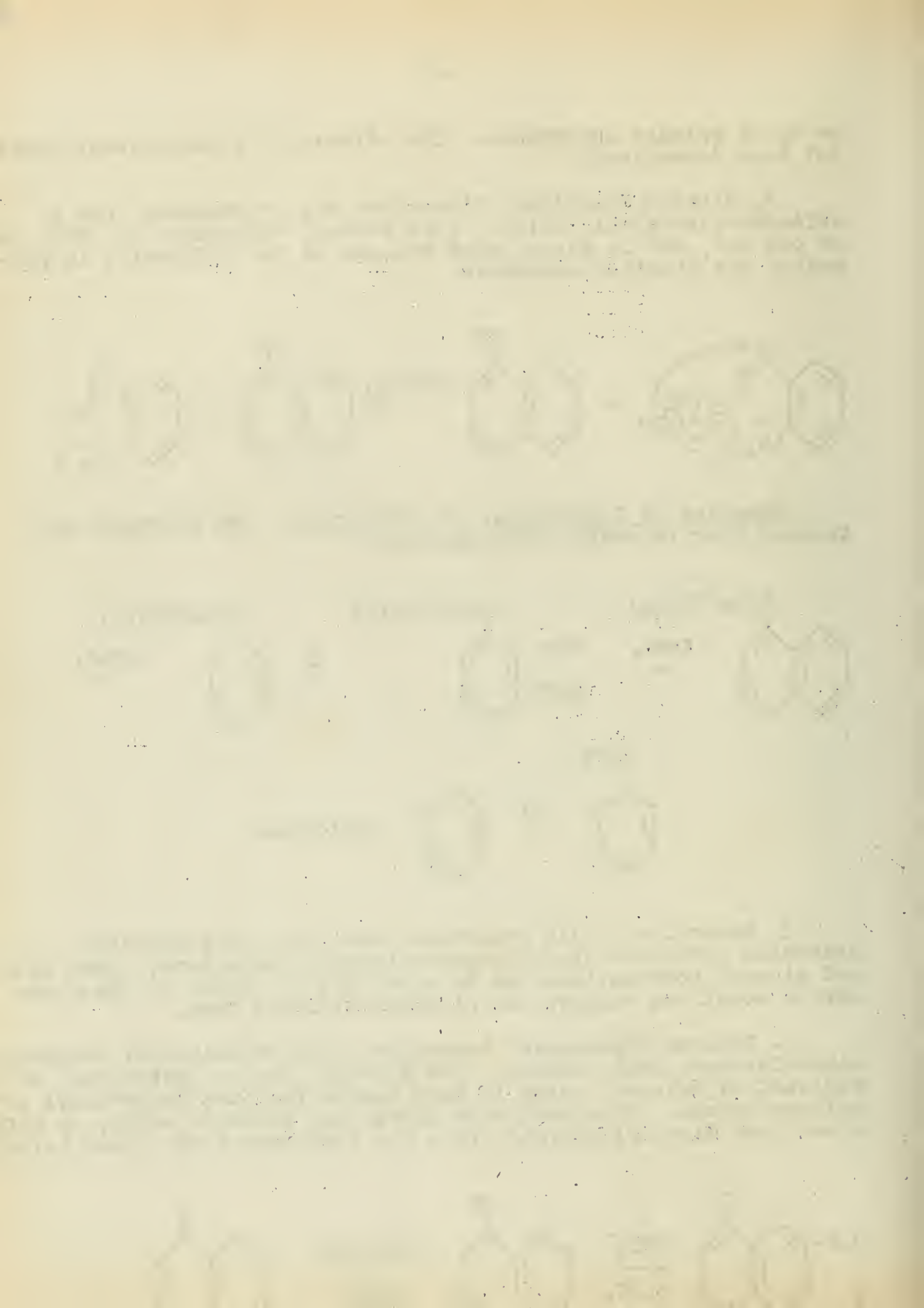


pyridazine

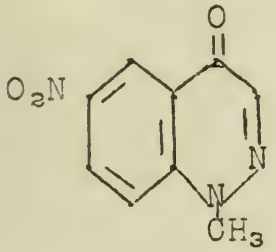
2. Reduction: Mild reduction with zinc and potassium hydroxide saturates the nitrogen-nitrogen double bond. Many metal and mineral combinations can be used, but an excess of these reagents sometimes cleaves the nitrogen-nitrogen bond.

3. Nuclear Replacement Reactions: The reactions of 4-hydroxycinnoline have been studied. The hydroxyl can be acetylated, or replaced by halogen, which in turn can be replaced by methoxyl or anilino groups. Treatment with nitric and sulfuric acids, or with alkali and dimethyl sulfate gives the transformations shown below.



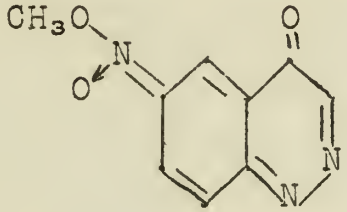


6-Nitro-4-hydroxycinnoline upon methylation with dimethyl sulfate gave a mixture of isomeric methyl ethers postulated as II and III.



II

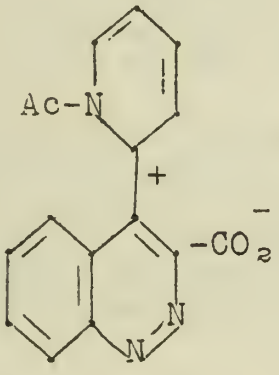
Pale yellow
M.P. 183°



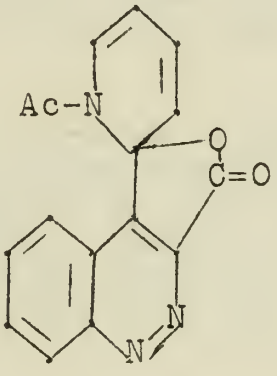
III

orange
M.P. 225°

4. Reaction with Pyridine and Acetic Anhydride: 4-Hydroxycinnoline-3-carboxylic acid, pyridine (or quinoline), and acetic anhydride, when heated together give a product postulated as IV or V. This reaction is specific for the 4-hydroxy-3-carboxylic acids. Without the carboxyl group, the hydroxyl is merely acetylated.



IV

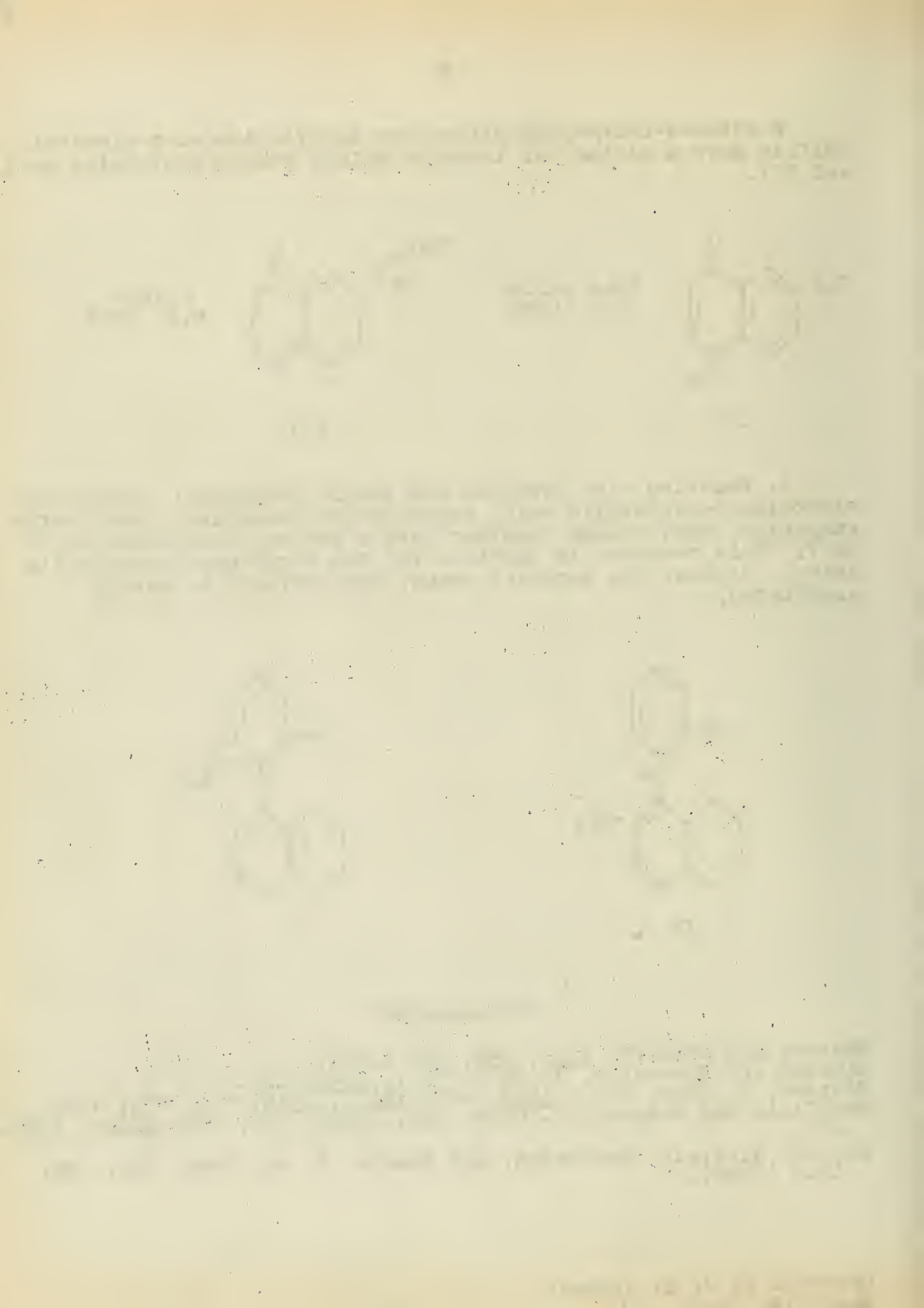


V

Bibliography

Borsche and Herbert, Ann., 546, 293 (1941).
Simpson and Stevenson, J. Chem. Soc., 1942, 353.
Simpson, J. Chem. Soc., 1943, 447; ibid., 1946, 480, 673, 1035.
Schofield and Simpson, J. Chem. Soc., 1945, 512, 520; ibid., 1946, 472.
Jacobs, Winstein, Henderson, and Spaeth, J. Am. Chem. Soc., 68, 1310 (1946).

Reported by J. L. Johnson
April 18, 1947



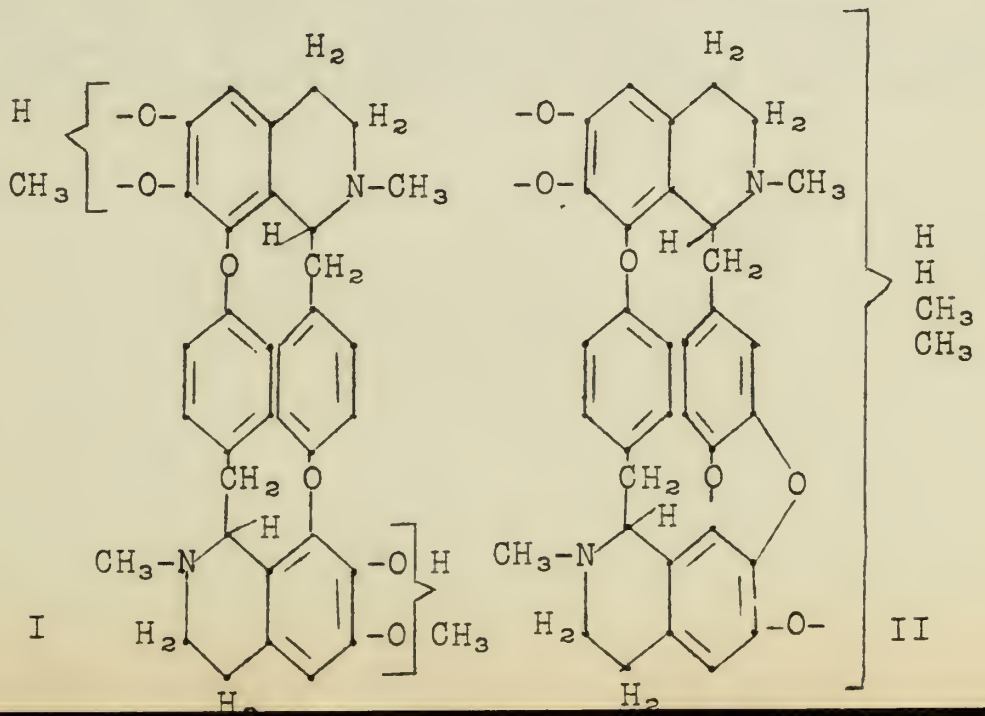
General.--Boehm (1) pointed out that the curares were of three kinds depending upon the method used for their storage. Tubocurare was the name given to that preparation which was put up in bamboo tubes. The name Calabash curare referred to that which was put up in gourds. The third type of curare was put up in earthenware crocks and called Potcurare.

Botanical origin.--The Tubocurare and potcurare are chiefly obtained from various species of Chondodendrons, whereas the Calabash curare is prepared from various species of Strychnos. Folkers (2) has shown that many species of the genus Strychnos possess curare-like activity, and Wintersteiner (3) has isolated a number of alkaloids from Chondodendron which had previously been found in Indian preparation of curare.

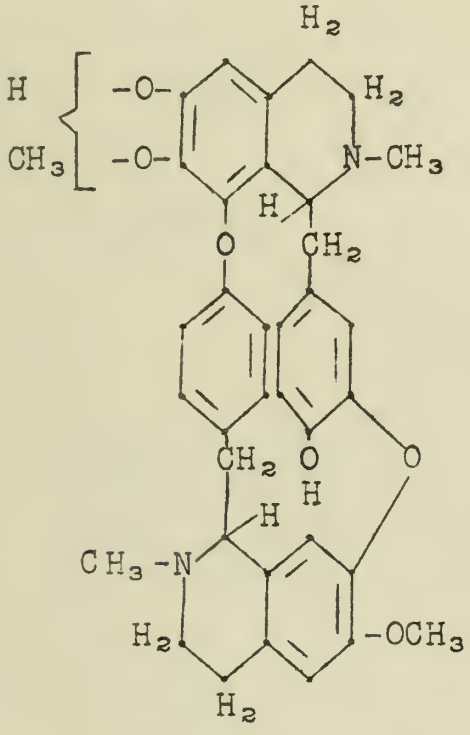
Physiological activity.--Curare has a powerful lissive (relaxing) action on the voluntary muscles. It is expected to become a valuable therapeutic agent in the treatment of spastic paralysis, convulsions, and shock. The nonuniformity of the crude preparations, their varying physiological activity, and uncertain chemical composition has restricted the useful exploitation of the material until recently.

Chemical constituents.--From Calabash curare, Wieland et al (4) has isolated and named the following products: C-curarine I, C-curarine II, C-curarine III, C-toxiferine, C-dihydrotoxiferine, C-isodihydrotoxiferine. The structures of these substances has not been elucidated, but the chemical reactions seem to indicate that they are of the strychnine type.

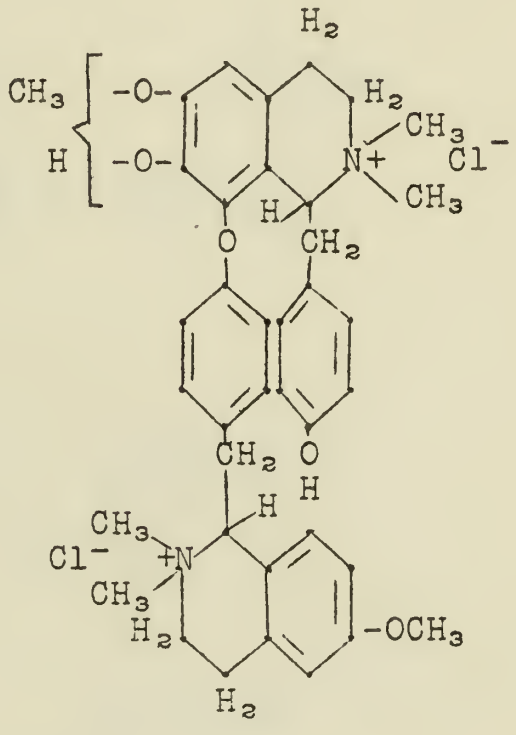
Boehm (1) obtained two quaternary bases from Potcurare which he called protocurine, m.p. 306°, and protocuridine, m.p. 275°. King (5) isolated an additional alkaloid from this same curare and called it neoprotocuridine, m.p. 232°. King has shown neoprotocuridine to have structure I, and protocuridine structure II. These substances have only mild curare-like activity.



Two closely related substances have been isolated from tubo curare. They are l-curine and d-tubocurarine chloride, structures III and IV respectively. This structure for curine was shown by Spath and Kuffner (6) on the basis of degradation experiments, and the tubocurarine chloride was isolated and its structure proven by King (5).

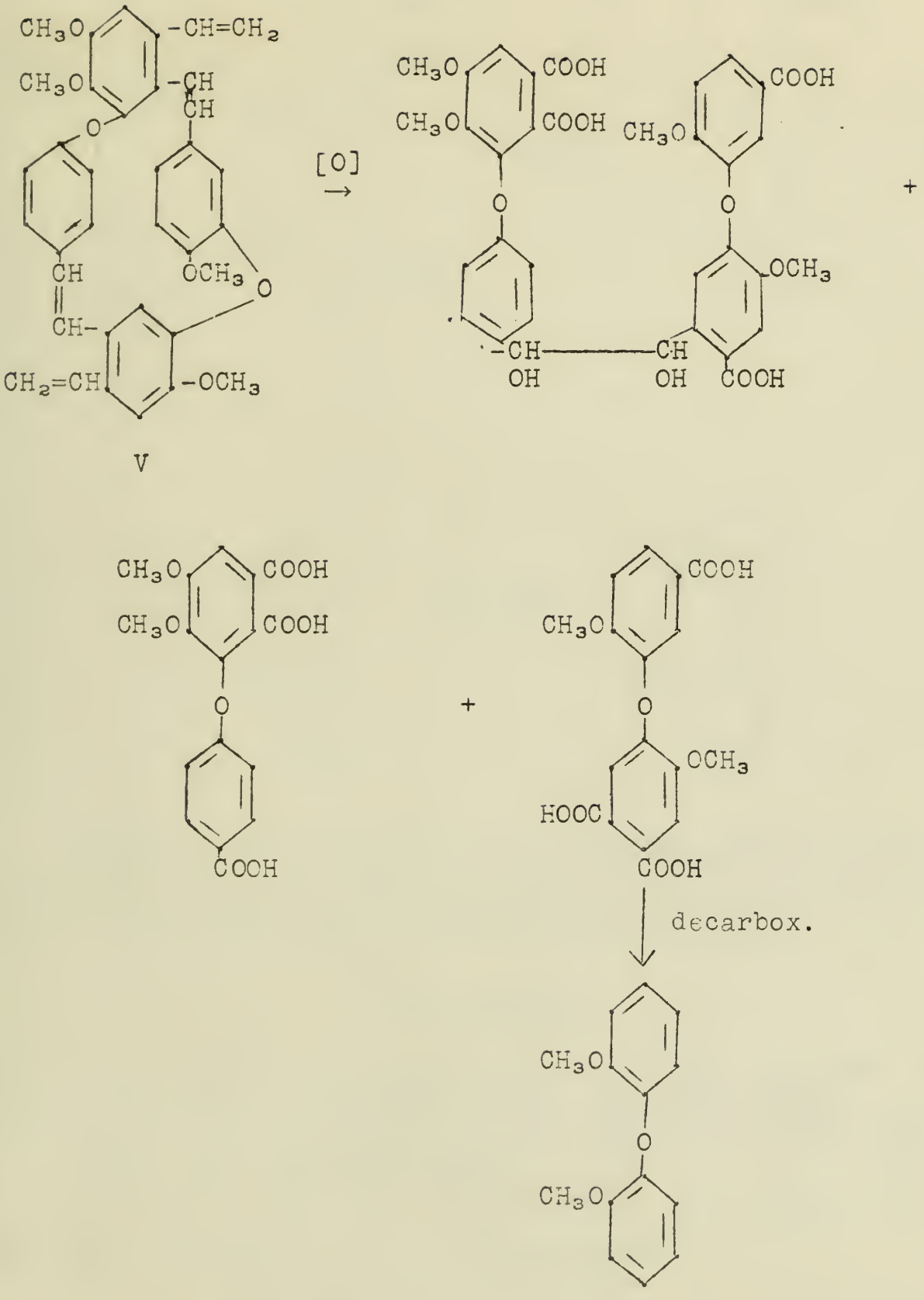


III



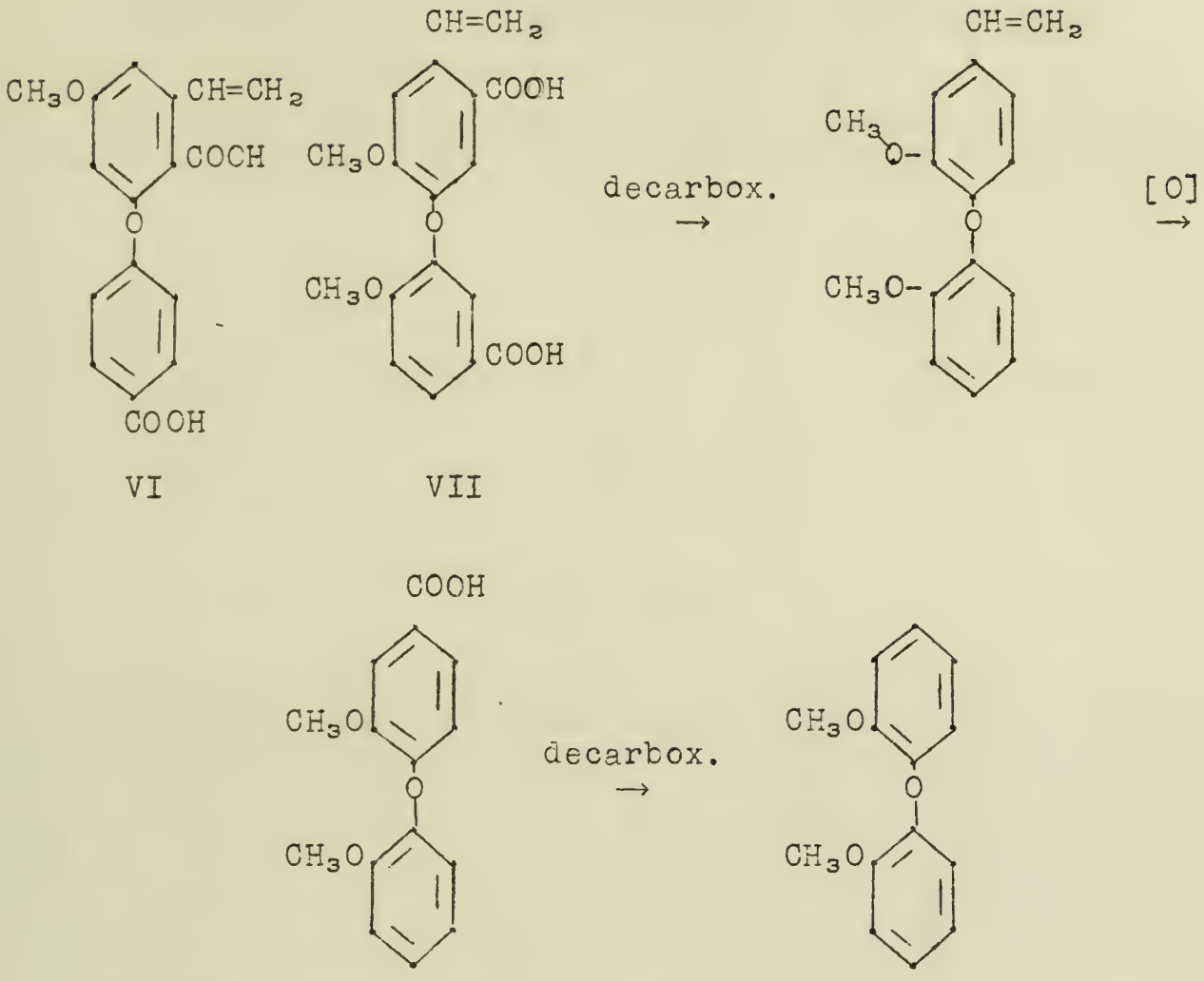
IV

Chemical degradation of tubocurarine.--Tubocurarine chloride upon methylation followed by one stage of Hofmann degradation yielded three methyl iodides found to be identical to three methyl iodides obtained by a similar degradation of d-bebeerine. It was shown that d-bebeerine upon methylation followed by two stages of Hofmann degradation yielded a substance V. Other reactions followed.



V

Faltis (7) obtained similar results by the degradation of structures VI and VII obtained from d-bebeerine by methylation followed by a Hofmann degradation, an ozonation, another methylation, and then another Hofmann degradation.



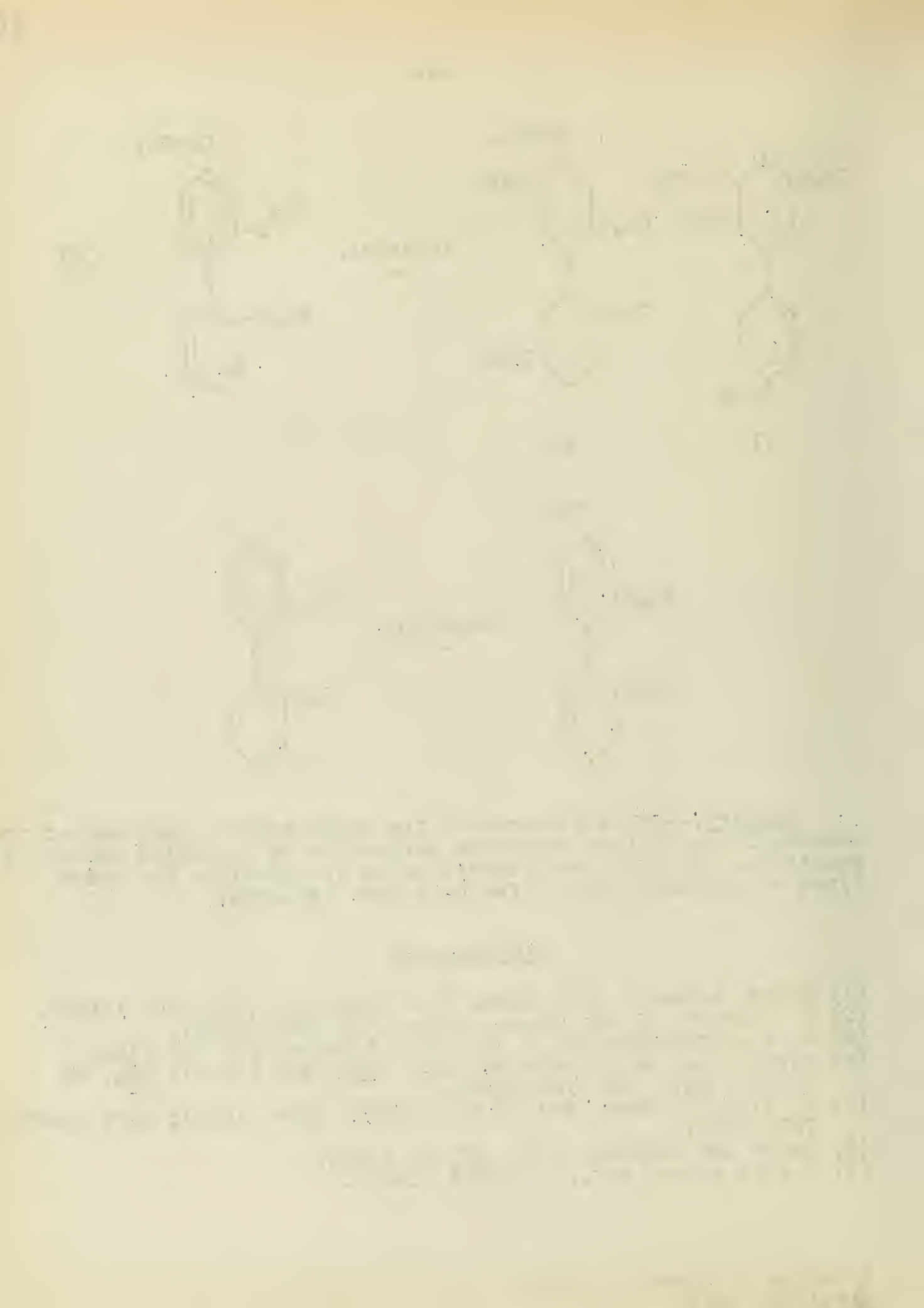
VI VII

Summary.--The structures of the other curare alkaloids of the bisbenzylisoquinoline type were arrived at by a similar series of reactions. Of the stereoisomers which are possible for these types of compounds only a few have been isolated.

Bibliography

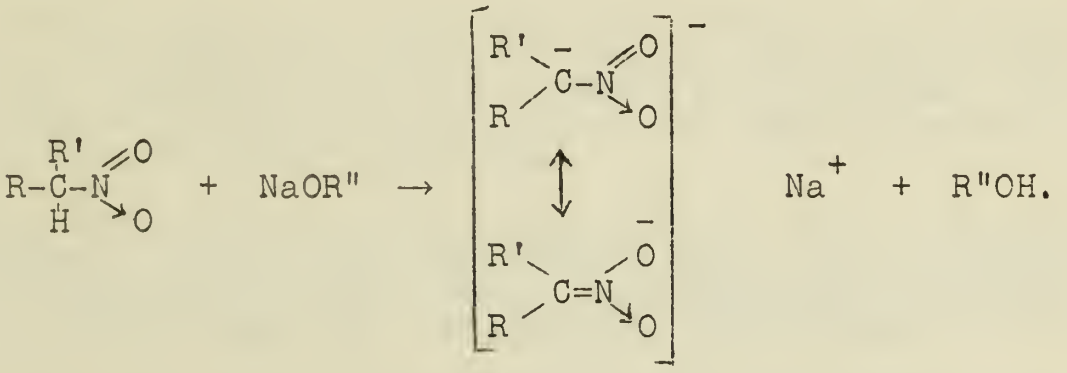
(1) Boehm, Abhandl. Kgl. Sachs Ges. Wissensch., 22, 203 (1895).
(2) K. Folkers, J. Am. Pharm. Assoc., 27, 689 (1938).
(3) O. Wintersteiner and J. Dutcher, Science, 97, 467 (1943).
(4) Wieland and collaborators, Ann., 527, 160 (1937); 536, 68 (1938); 547, 140, 156 (1940).
(5) H. King, J. Chem. Soc., 1381 (1935); 1276 (1936); 1472 (1937); 737 (1940).
(6) Spath and Kuffner, Ber., 67, 55 (1934).
(7) Faltis et al, Ber., 69, 1269 (1936).

Reported by Viron V. Jones
April 25, 1947



THE BASIS FOR THE REPORTED OPTICAL ACTIVITY OF THE SALTS OF ALIPHATIC NITRO COMPOUNDS: 2-NITROÖCTANE[1]

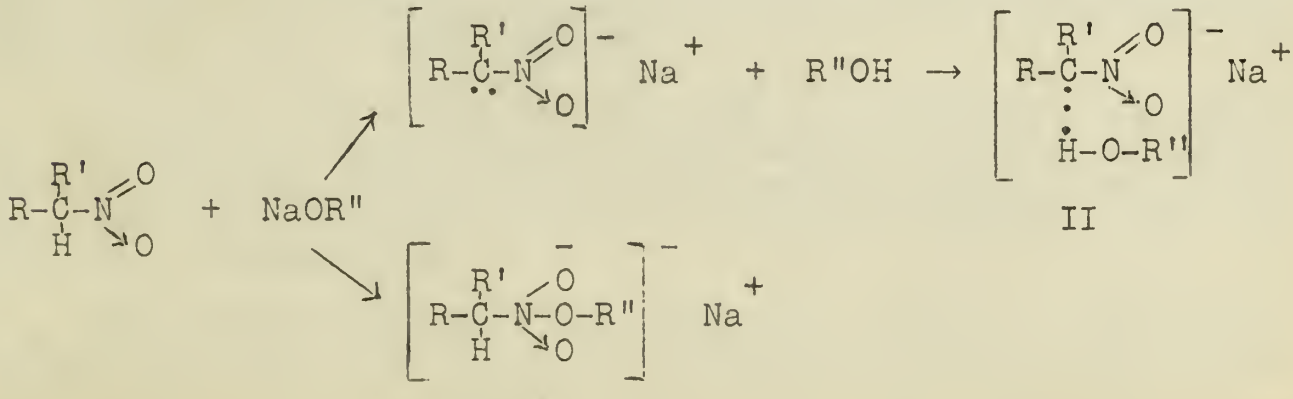
Aliphatic nitro compounds having an α-hydrogen atom are readily soluble in alkali, presumably according to the equation



I

Apparently contradicting the struction of ion I, it was reported[2] in 1927 that optically active 2-nitrobutane gave an optically active sodium salt when treated with sodium methoxide. This salt was transformed by the action of bromine into optically active 2-bromo-2-nitrobutane. These findings were confirmed[3] in 1930 by a similar study using optically active 2-nitroöctane. Here again optically active sodium salts were obtained which gave optically active 2-bromo-2-nitroöctane on treatment with bromine. In addition, the active sodium salts were converted back to active 2-nitroöctane having about 24% of the original rotation.

This unexpected retention of configuration by the salts of nitroparaffins cast a rather serious doubt on the structure of ion I, since a resonance hybrid of this kind would be planar and therefore not capable of optical asymmetry. Consequently alternative structures were proposed for this ion in which the asymmetry of the carbon atom is retained either by coördination with a solvent molecule (II), or by leaving the asymmetric center unaffected (III).



II

III

It occurred to Kornblum and coworkers that the observed partial retention of optical activity of the regenerated 2-nitrooctane might be explained by assuming competing reactions forming a mixture of ions I (racemization) and III (retention of asymmetry).

If optically active 2-nitrooctane having a deuterium atom in place of the α-hydrogen atom were treated with sodium methoxide, and if the competing reactions occurred as postulated, then the regenerated 2-nitrooctane should show the same percentage loss of optical activity and of deuterium.

This work was not carried out, however, for it became apparent to Kornblum in preliminary experiments that the 2-nitrooctane prepared as described by the previous investigators contained some optically active impurity. These facts were noted:

1. When the material was shaken with 10% aqueous sodium hydroxide, about 25% failed to dissolve, even on repeated treatment with alkali.

2. The d-2-nitrooctane used had a lower specific rotation than the levo isomer (because of partial racemization during its preparation), but formation of the alkali salts of the two isomers, followed by regeneration with acid, gave products with the same residual activity.

3. When the regenerated material (retaining 24% of the original rotation) was subjected to the alkali-acid cycle a second time, it underwent no further loss of rotation.

Because of the evident impurity of the material prepared by the reaction of 2-bromooctane with silver nitrite, a careful investigation of the products was carried out. In addition to the desired 2-nitrooctane and the expected 2-octyl nitrite, at least three other compounds were present. 2-Octanol, 2-octanone and 2-octyl nitrate were identified, the last of which cannot be separated from 2-nitrooctane by fractional distillation (the procedure used in the earlier investigation). Thus the "2-nitrooctane" used previously was contaminated with 2-octyl nitrate, and the optical activity ascribed to the salts of 2-nitrooctane was actually due to this impurity.

To remove the impurities from the 2-nitrooctane, the mixture was stirred with five volumes of 96% sulfuric acid at 0° and the colored solution poured onto ice covered with petroleum ether. The ether extracts were extracted with 85% phosphoric acid, then dried and fractionated.

The purified material was completely soluble in 10% aqueous sodium hydroxide solution, and the resulting solution was devoid of optical activity. 2-Bromo-2-nitrooctane was obtained on bromination of the sodium salt and it was also completely inactive. Ethanolic sodium ethoxide had the same effect as the sodium

hydroxide, and the 2-nitrooctane regenerated on acidification of the sodium salt was completely racemic.

Thus it should probably be concluded that the anion of the alkali salts of the nitroparaffins has essentially the resonating planar structure represented by I.

Bibliography

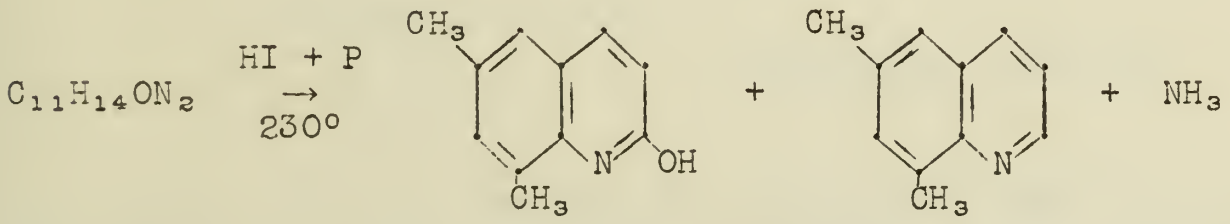
1. Kornblum et al., J. Am. Chem. Soc., 69, 307 (1947).
2. Kuhn and Albrecht, Ber., 60, 1297 (1927).
3. Shriner and Young, J. Am. Chem. Soc., 52, 3332 (1930).
4. Gilman, ed. "Organic Chemistry", Wiley, New York, 1943, Vol. I, p. 391.
5. Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen", Clarendon Press, Oxford, 1937, p. 239.

Reported by Francis Warren Blodgett
April 25, 1947

CYTISINE

Cytisine is the natural alkaloid of the ornamental laburnum tree and many other plants and woods. Its physiological activity is very similar to that of nicotine although the two compounds are not chemically related. Local anaesthetics which have pronounced activity but less toxicity than cocaine have been synthesized from cytisine (1).

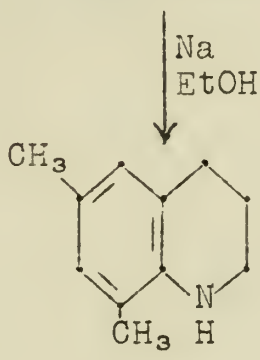
The compound was first isolated in 1865 and its first known reactions are outlined below (2,3,4).



Cytisine

Cytisoline ($C_{11}H_{11}ON$)

β-Cytisolidine ($C_{11}H_{11}N$)

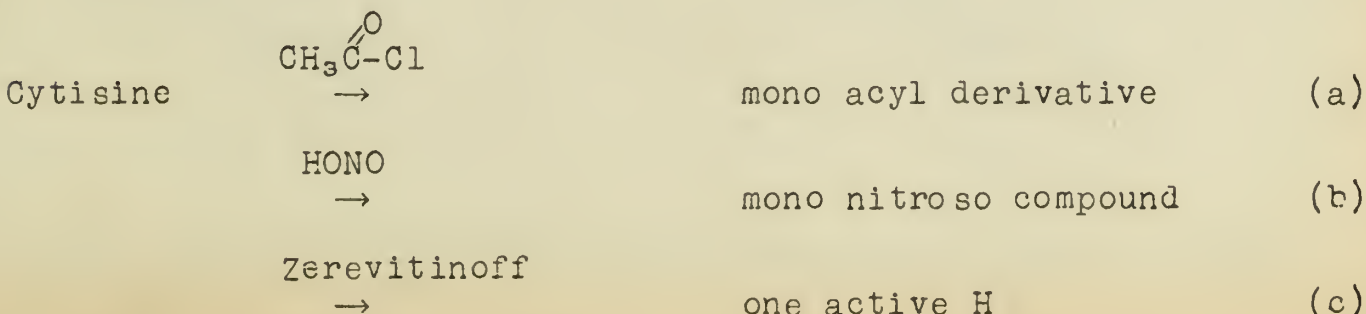


α-Cytisolidine ($C_{11}H_{15}N$)

H_2SO_4 → HNO_3 (1 drop)

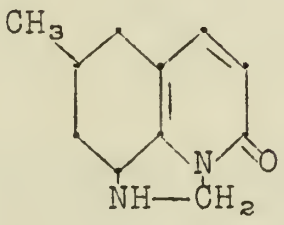
Carmine-red color typical of substituted tetrahydroquinolines.

Examination of the empirical formula of cytisoline showed that in cytisine itself there was a nitrogen atom still to be accounted for, the nature and position of which was unknown. Other workers (5,6) carried out the reactions outlined in equations (a) through (g).



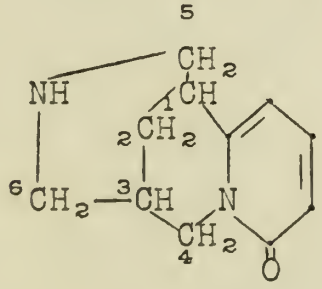
HCl or HBr → 200 - 250°	no decomposition	(d)
Carbonyl reagents →	no reactions	(e)
$KMnO_4$ →	no benzene carboxylic acids	(f)
Hofmann Exhaustive → Methylation	$C_{22}H_{22}O_2N_2 + (CH_3)_3N$	(g)

On the basis of equations (a) through (e) Späth reasoned that the oxygen in cytisine might be an α-pyridone type. He postulated structure I for the alkaloid, from which cytisoline could arise by the migration of a methyl group to position 8 together with the expulsion of ammonia (7).



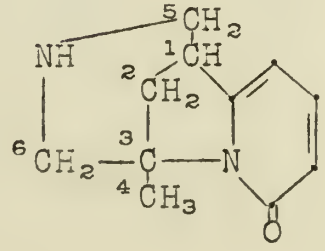
I

On the other hand, from the data of equations (f) and (g), Ing suggested that perhaps the quinoline nucleus did not appear as such in cytisine at all, but that the alkaloid was a substituted pyridone such as



A

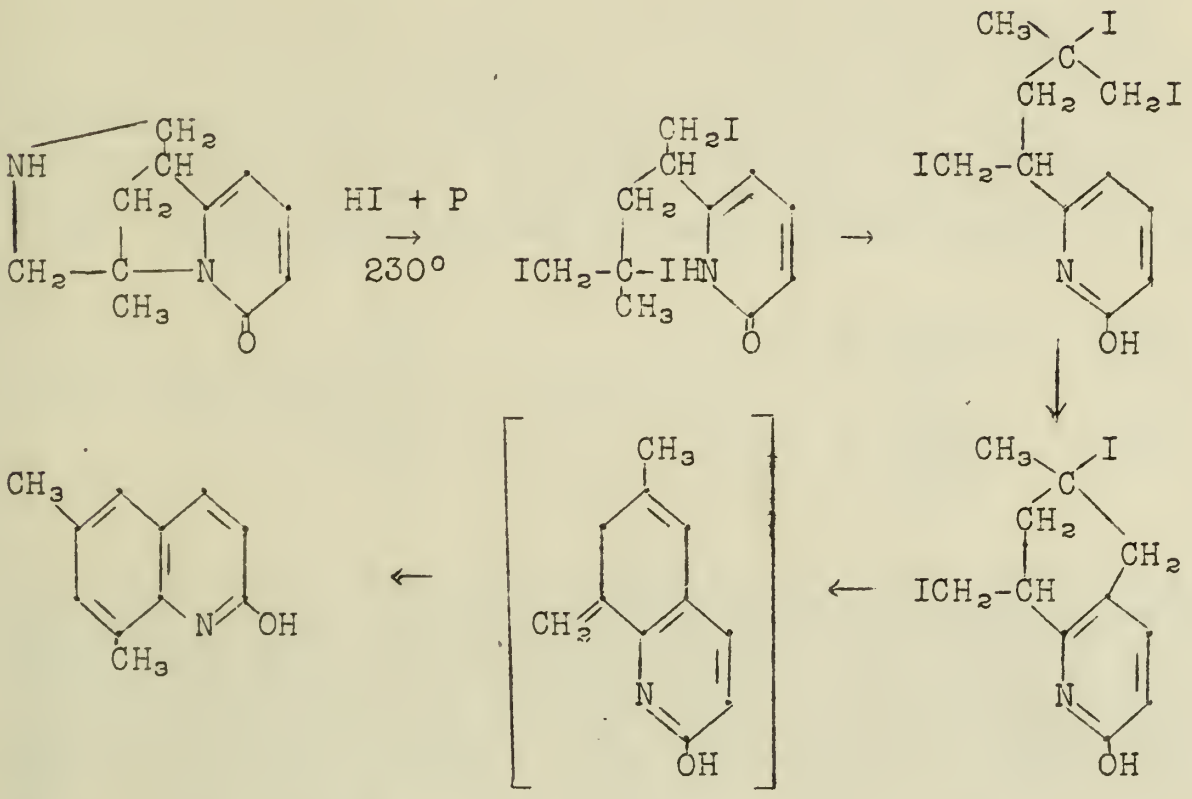
or



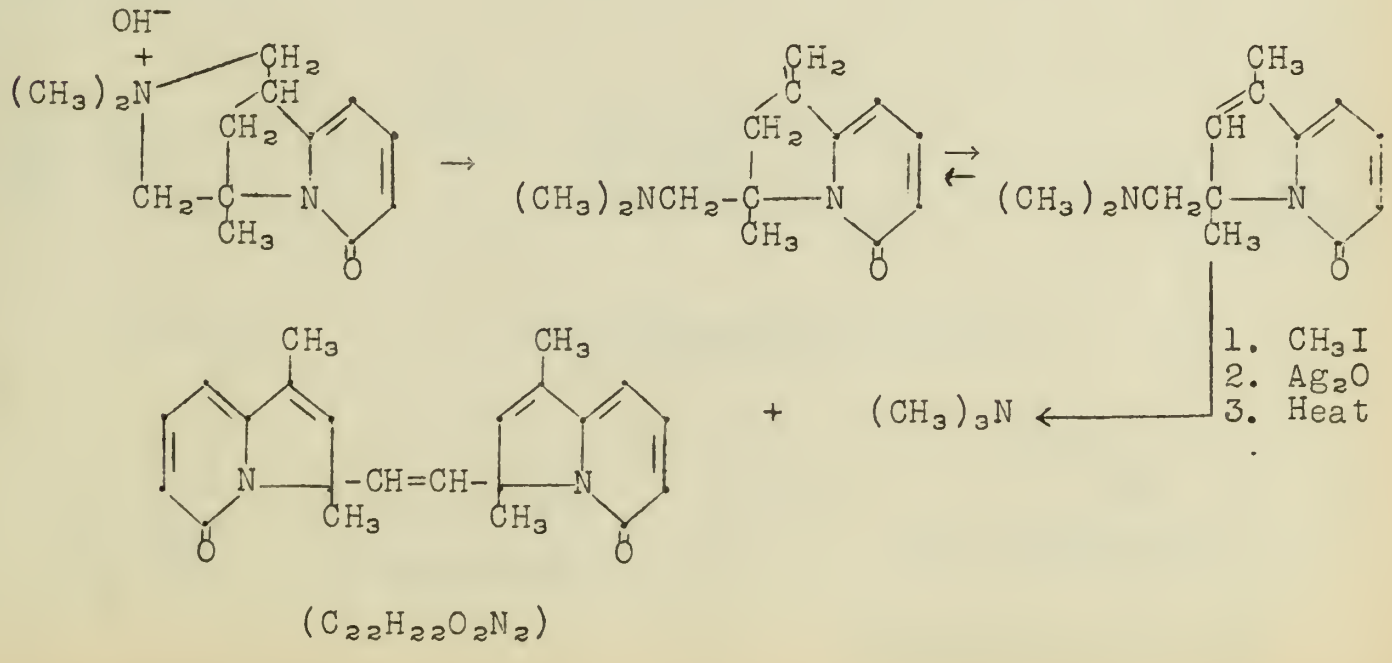
B

On this basis the action of HI and phosphorus to give a 6,8-dimethylquinoline seemed possible since these reagents are known

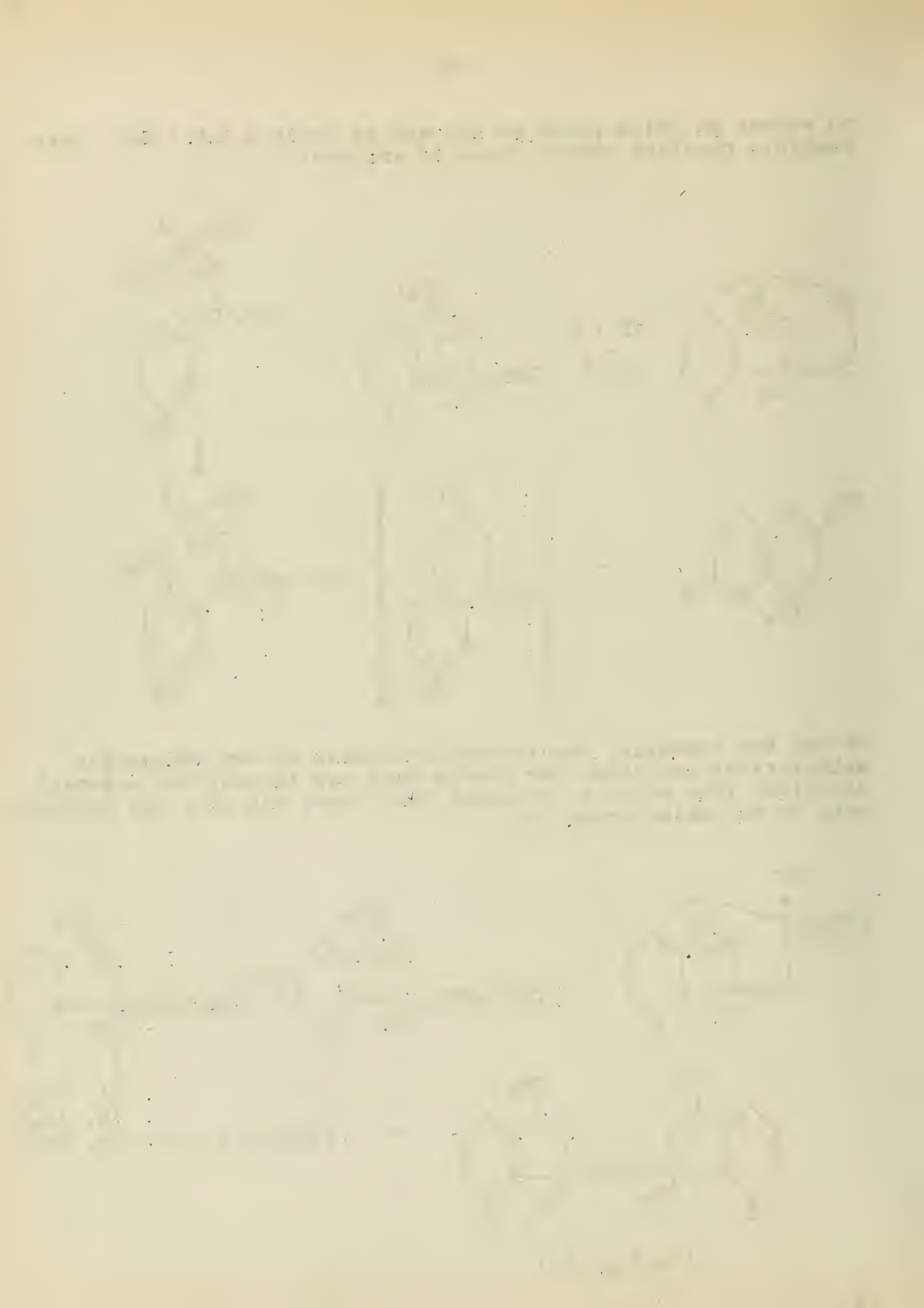
to remove an imino group as NH_3 and to break a C-N link. This complete reaction series could be written:



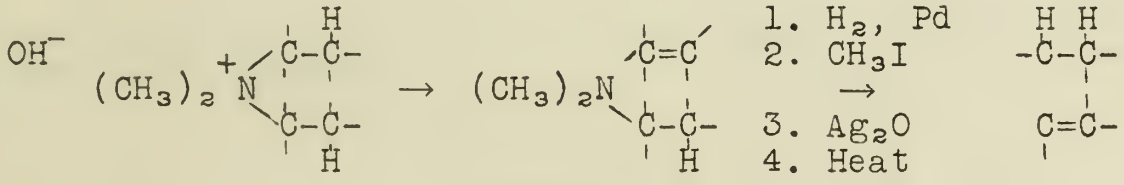
Of the two formulae, Ing favored B because on two exhaustive methylations and after one double bond was formed, the material dimerized from which he reasoned that there was only one hydrogen beta to the amino group (8).



$(C_{22}H_{22}O_2N_2)$

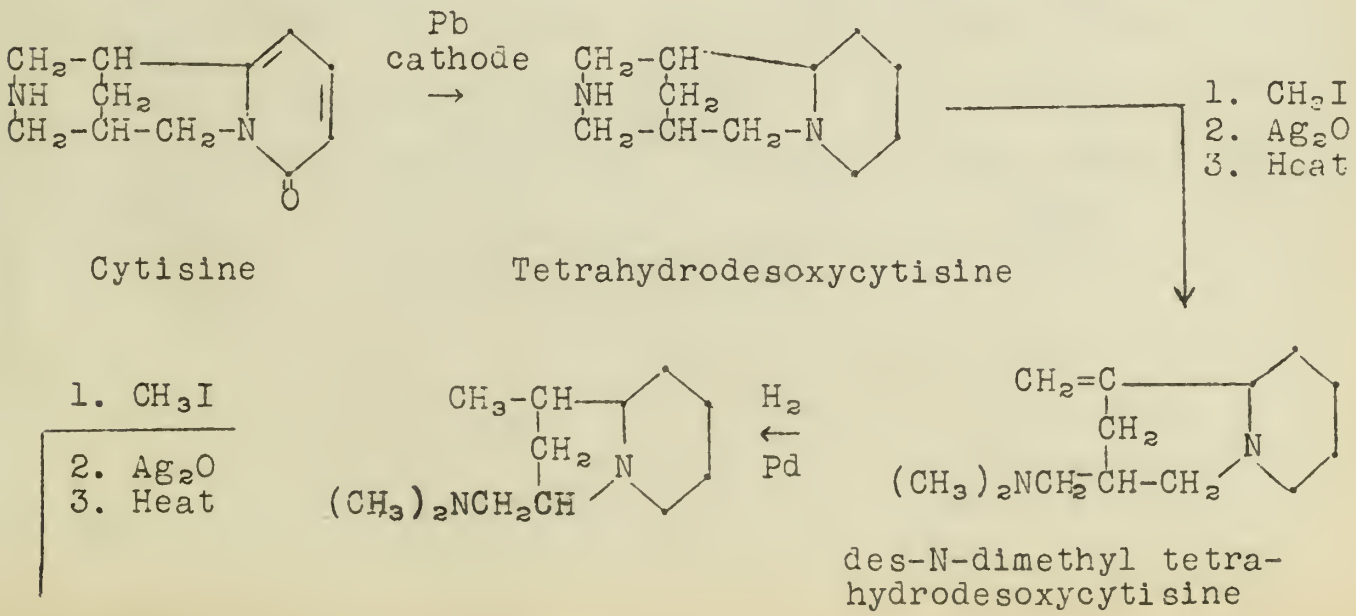


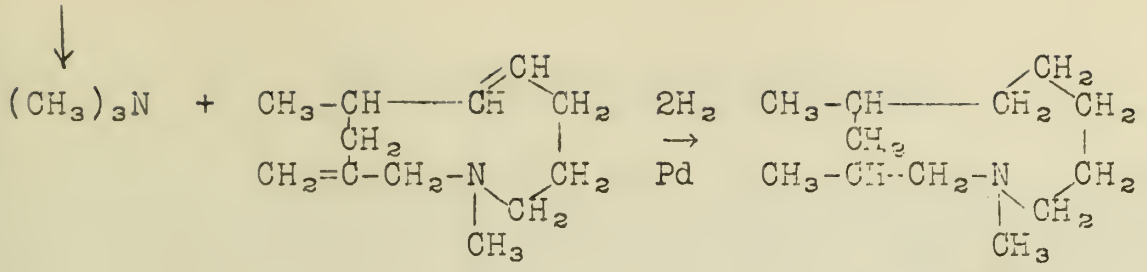
Subsequent work by Späth, however, showed that the appearance of the dimerization product which Ing obtained had been interpreted incorrectly. By conducting a Hofmann degradation under special conditions he showed that methylcytisine methohydroxide lost water on heating in vacuo at 90° to yield an unsaturated base. This was then hydrogenated catalytically to the dihydro compound and again subjected to the degradation. This step went smoothly to give trimethylamine and another unsaturated base. This showed that the hydrogenated ring must have had hydrogen atoms in both beta positions to the N atom, a condition not fulfilled by Ing's structure B (9). These reactions may be shown schematically as follows.



Späth also showed by a Herzig-Meyer test that the hydrogenated product of the second degradation had no N-methyl quinoline system, indicating that the N of this compound was common to two rings. This was confirmed by reducing cytisine at the Pb cathode to tetrahydrodesoxycytisine which after a degradation-reduction-degradation cycle yielded a base exhibiting two double bonds and one N-methyl group. This indicated that (a) an -NH in cytisine was split off with the formation of a double bond, (b) a ring of which the tertiary N atom was a part was broken open, and (c) no N-methyl was present in cytisine or hydrogenated cytisine.

From this work formula B was abandoned and these reactions are illustrated with formula A, which is the accepted structure for cytisine.





$C_{12}H_{25}N$

Other workers have substantiated this structure for cytisine (10-15).

All attempted syntheses of this alkaloid have so far been unsuccessful (16-18).

Bibliography

(1) Ing and Patel, J. Chem. Soc., 1936, 1774-1775.
(2) Freund, Ber., 34, 615 (1901); 37, 16 (1904); 39, 814 (1906).
(3) Ewins, J. Chem. Soc., 1913, 97-104.
(4) Späth and Galinovsky, Monatsch., 40, 93-128 (1919).
(5) Partheil, Ber., 23, 3201 (1890).
(6) Ing, J. Chem. Soc., 1931, 2195-2203.
(7) Späth, loc. cit., 15-33.
(8) Ing, loc. cit.
(9) Späth and Galinovsky, Ber., 65B, 1526-1535 (1932).
(10) Ing, J. Chem. Soc., 1932, 2778-2780.
(11) Späth and Galinovsky, Ber., 66B, 1334-1344 (1933).
(12) Ibid., 69B, 761-766 (1936); 721-724 (1936).
(13) Ibid., 76B, 947-949 (1943).
(14) Polonovski and Lecoq, Compt. Rend., 214, 912-14 (1942); Chem. Abs., 38, 4265.
(15) Lecoq, Bull. Soc. Chem., 10, 153-160 (1943); Chem. Abs., 38, 3891.
(16) Chakravarti and Venkattosubban, J. Ammalai Univ., 2, 227-237 (1933); Chem. Abs., 28, 2008.
(17) Chakravarti and Rao, ibid., 5, 254-8 (1936); Chem. Abs., 28, 2008.
(18) Mitra, J. Indian Chem. Soc., 15, 455-461 (1938).

Reported by Johnnie Mirza
April 25, 1947

STERIC INHIBITION OF RESONANCE

If an aromatic amine or nitro compound has a bulky ortho substituent, the steric hindrance thus produced tends to prevent coplanarity and thus inhibits resonance. Thus the carbon to nitrogen bond will have less double bond character and the group will have a smaller activating effect on the ring. This phenomenon explains many chemical and physical properties of compounds in which resonance is sterically hindered.

Compounds such as 4,6-dinitro-m-xylene and 2,4,6-trinitro-m-xylene will condense with benzaldehyde in the presence of piperidine whereas dinitro and trinitromesitylene in which each nitro group has two methyl groups in the ortho position fail to undergo this condensation.[1]

Verkade found that ortho- or para-nitroacetanilides could be deacetylated by heating in ethanol containing 3 molar per cent of sodium ethylate. However, if ortho substituents hinder either the nitro or acetamido group from becoming coplanar with the benzene ring, the compound fails to undergo the reaction.

From a study of reaction constants, Holleman[6] found the chlorine in 2,6-dichloronitrobenzene to be less reactive toward sodium methylate than were the 2,3; 2,5; 3,4; and 2,4 isomers.

In phenols the contribution of those resonance hybrids which have the quinoid structure favors the ionization of the compound.[8] One function of a nitro group in an ortho- or para-position is to enhance resonance so that the quinoid structure makes a larger contribution which in turn would increase the acidity of the compound. If the nitro group were sterically hindered from becoming coplanar with the ring, the effect due to resonance would be diminished. Table I shows that this is found to be true experimentally.

TABLE I[8]

Compound	pKa	Compound	pKa	△ pKa
phenol	9.97	p-nitrophenol	7.21	2.76
m-2-xylenol	10.60	5-nitro-m-2-xylenol	7.16	3.44
m-5-xylenol	10.09	2-nitro-m-5-xylenol	8.24	1.85

In aromatic amines, resonance would stabilize the molecule with respect to the ion. Thus if the resonance of an aromatic amine is inhibited, the compound becomes more basic. This is shown by Table II.

TABLE II[3,4,7,8]

RNH_2	pK_a of RNH_2	pK_a of $RN(CH_3)_2$	Δ pK_a	pK_a of $RN(C_2H_5)_2$	Δ pK_a
	(water solution)				
aniline	4.58	5.06	0.48	6.56	1.98
o-toluidine	3.39	5.86	1.47	7.18	2.79
p-toluidine	5.12	5.50	0.38	7.09	1.97
	(50 per cent ethanol solution)				
aniline	4.25	4.26	0.01		
o-toluidine	3.98	5.07	1.09		
m-2-xylidine	3.42	4.69	1.27		
m-4-xylidine	4.61	5.28	0.57		
m-5-xylidine	4.30	4.48	0.18		
p-xylidine	4.17	5.19	1.02		

In aromatic amines and nitro compounds resonance would tend to increase the dipole moment.[8] The dipole moments of various substituted benzenes, durenes, and mesitylenes are listed in Table III. In the compounds containing bromine no steric inhibition of resonance can occur, and the moments are about the same; whereas in the nitro and dimethylamino substituted mesitylenes and durenes the moment is smaller than that of the corresponding benzene derivative in every case.

TABLE III[2,5,8]

X	Y	p-C_6H_4XY	$C_6(CH_3)_4XY$ (durene)	$C_6H_2(CH_3)_3X$ (mesitylene)
NO_2	H	3.95	3.39	3.64
$N(CH_3)_2$	H	1.58	----	1.03
NH_2	H	1.53	1.39	1.40
Br	H	1.52	1.55	1.52
NO_2	$N(CH_3)_2$	6.87	4.11	
NO_2	NH_2	6.10	4.98	

Table IV shows that the substitution of a nitro or dimethylamino group on an aromatic ring causes a smaller increase in the molar refractivity if one or both of the ortho positions are substituted. In each case the atomic refractivity of the entering group is nearer to the value it would have in an aliphatic compound.

TABLE IV[7]

Compound	$(R_L)D$	Δ	Compound	$(R_L)D$	Δ
benzene	26.18		benzene	26.17	
nitrobenzene	32.74	6.56	dimethylaniline	40.45	14.68
mesitylene	40.76		m-xylene	35.93	
nitromesitylene	46.98	6.22	dimethyl-m-5-xylidine	50.58	14.65
1,3-dichlorobenzene	36.16		dimethyl-m-4-xylidine	49.55	13.62
5-nitro-	42.94	6.78	dimethyl-m-2-xylidine	48.99	13.06
2-nitro-	42.32	6.16	p-xylene	35.95	
chloroform	21.40		dimethyl-p-xylidine	49.61	13.62
chloropicrin	27.32	5.92	toluene	31.06	
chlorobenzene	31.38		dimethyl-p-toluidine	45.68	14.62
dimethyl-o-chloro-			dimethyl-m-toluidine	45.68	14.62
aniline	44.95	13.57	dimethyl-o-toluidine	44.62	13.56

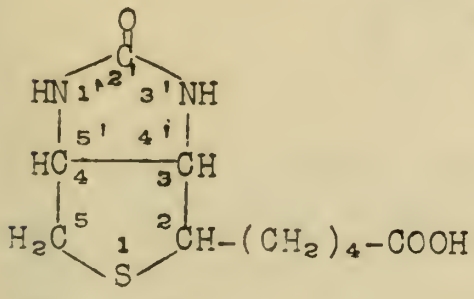
Bibliography

(1) Borsche, Ann., 386, 351 (1912).
(2) Brown, de Bruyne, and Gross, J. Am. Chem. Soc., 56, 1291 (1934).
(3) Davies and Addis, J. Chem. Soc., 1937, 1622.
(4) Hall and Sprinkle, J. Am. Chem. Soc., 54, 3469 (1932).
(5) Hamson and coworkers, J. Chem. Soc., 1937, 10; 1939, 981.
(6) Holleman, Rec. trav. chim., 35, 19 (1915).
(7) Thomson, J. Chem. Soc., 1944, 405, 408; 1946, 1113.
(8) Wheland, The Theory of Resonance, John Wiley and Sons, N. Y. (1944).

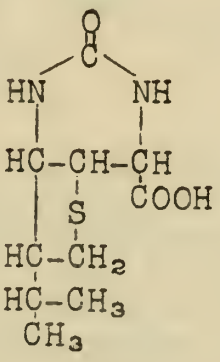
Reported by George Munn
May 2, 1947

RECENT STUDIES IN BIOTIN SYNTHESIS

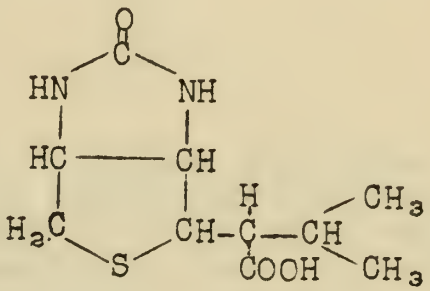
Biotin, a member of the Vitamin B Complex group, has been shown to possess structure I (1,2). Since one synthesis of biotin has been presented previously (3), this seminar will discuss only some of the recent studies involved in two additional syntheses of biotin.



I



II

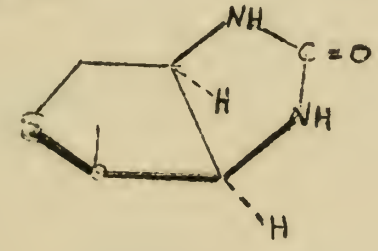


III

α- and β-Biotin.--It has been shown recently (4) that a second yeast growth factor may be isolated from egg yolk with similar physiological functions but with one-half the yeast growth activity of I. The structure of this material has not been fully determined but Kögl (5) has proposed structures II or III with the most recent work favoring III.

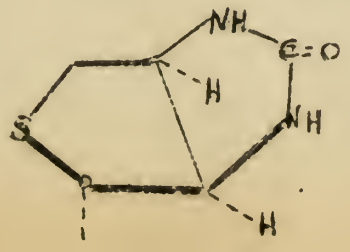
Kögl has suggested that the substance isolated from egg yolk be designated as "α-biotin" and that from liver (I) as "β-biotin." The German literature uses this terminology but these terms do not appear in the American journals. In this seminar we shall discuss only the compound represented by structure I, known in the American journals simply as biotin.

Stereochemistry of Biotin.--Biotin contains three asymmetric carbon atoms (carbons 2, 3, 4 in structure I) and could theoretically exist in eight stereoisomeric forms. Schematically these eight forms (four racemic mixtures) may be represented as follows:



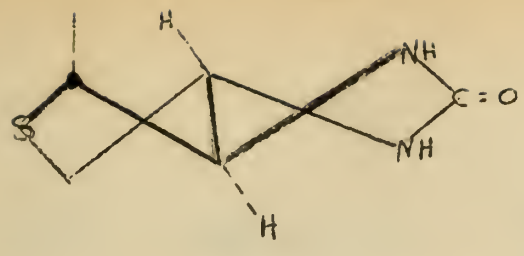
(dl)

A

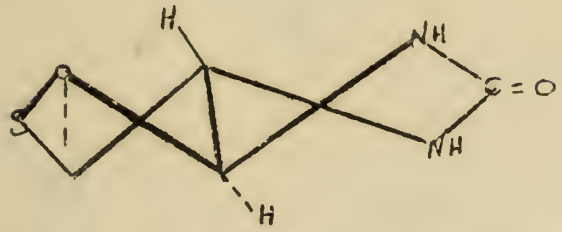


(dl)

B



(dl)
C

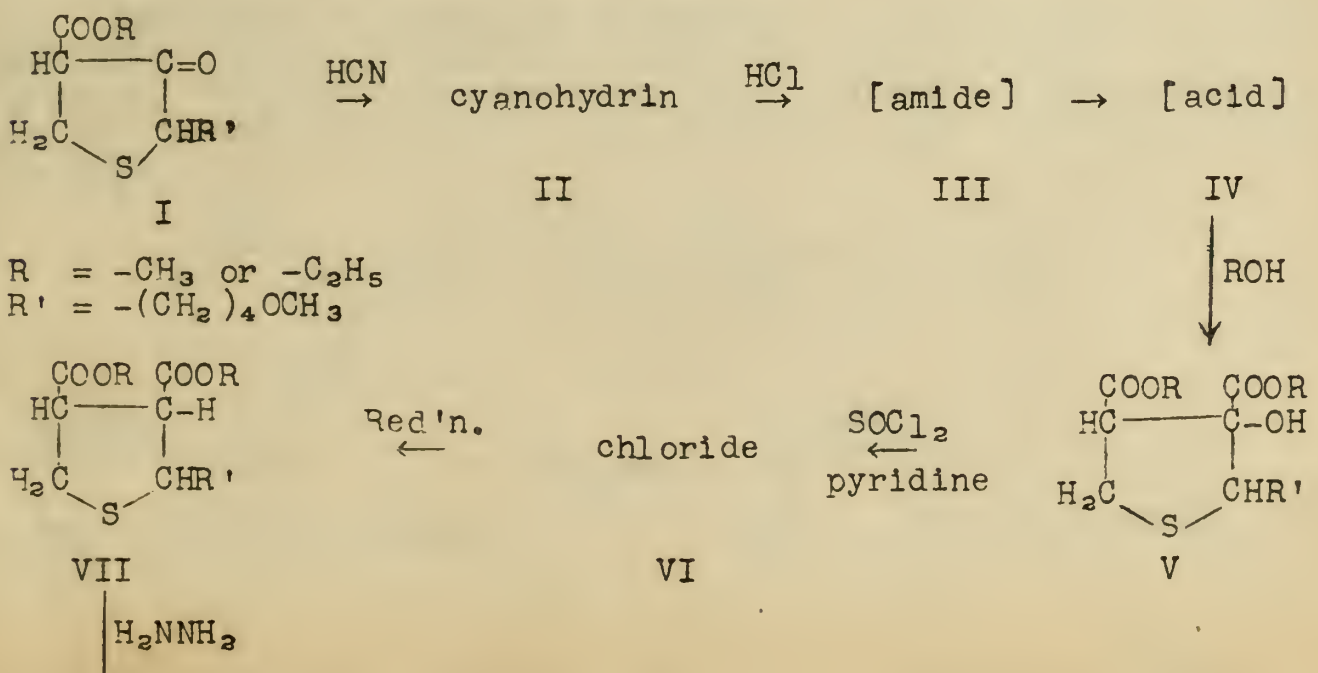


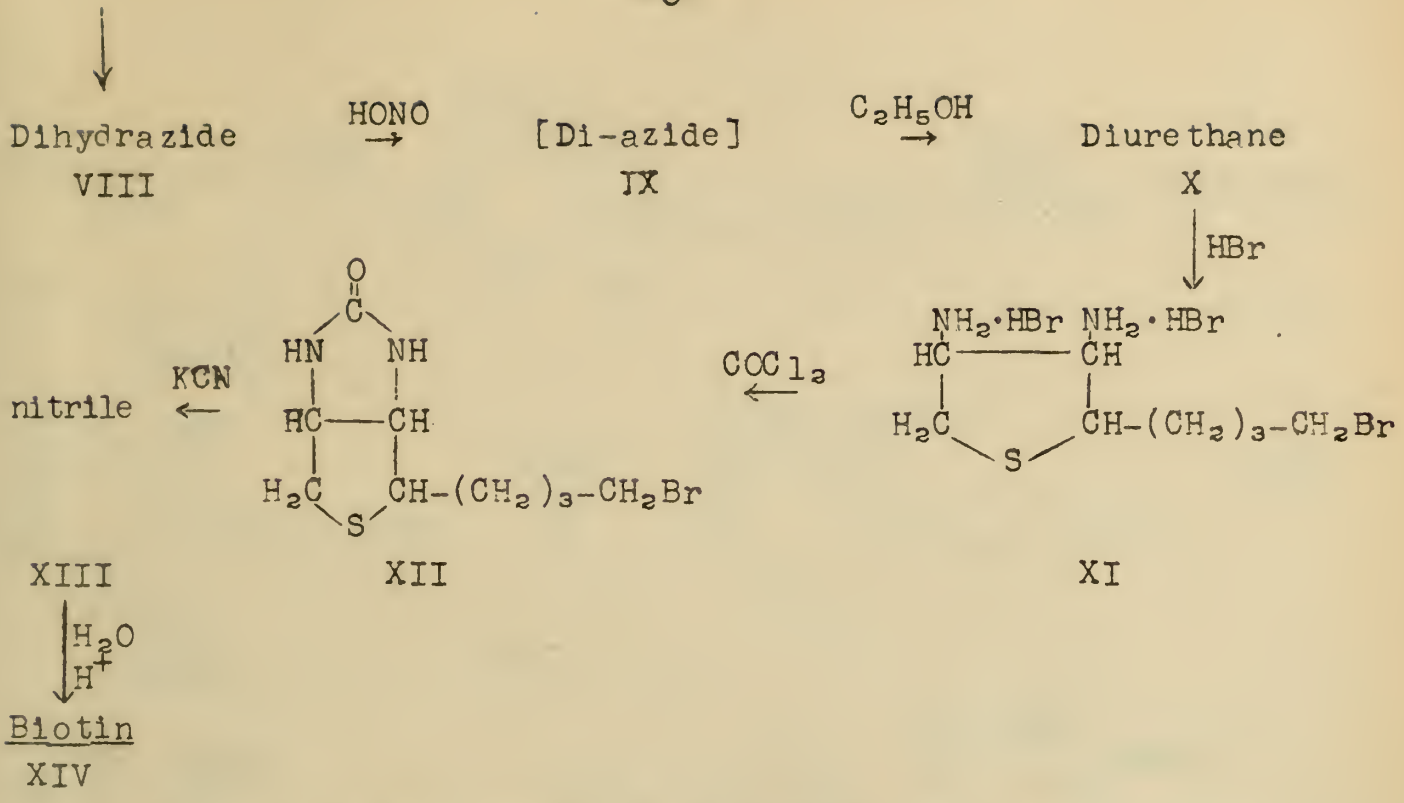
(dl)
D

In structures A and B the two rings (thiophane and imidazolidone) bear a cis relationship to each other with the side chain above the plane of the thiophane ring in A and below the plane in structure B. Both A and B represent the less strained arrangements of the biotin molecule. Structures C and D, representing the corresponding trans configurations of the fused rings, are more highly strained molecules and are comparatively unstable.

The Merck group had obtained, by their synthetic procedure (3), three of the above four possible racemic mixtures (6,7). dl-Biotin was found to belong to the series in which the thiophane and the imidazolidone rings are cis to each other (A or B), while the other two isomers which were isolated (dl-allobiotin and dl-epiallobiotin) were found to belong to the trans system (C and D). At the present time the configuration of the side chain about carbon 2 in all of these structures is not known.

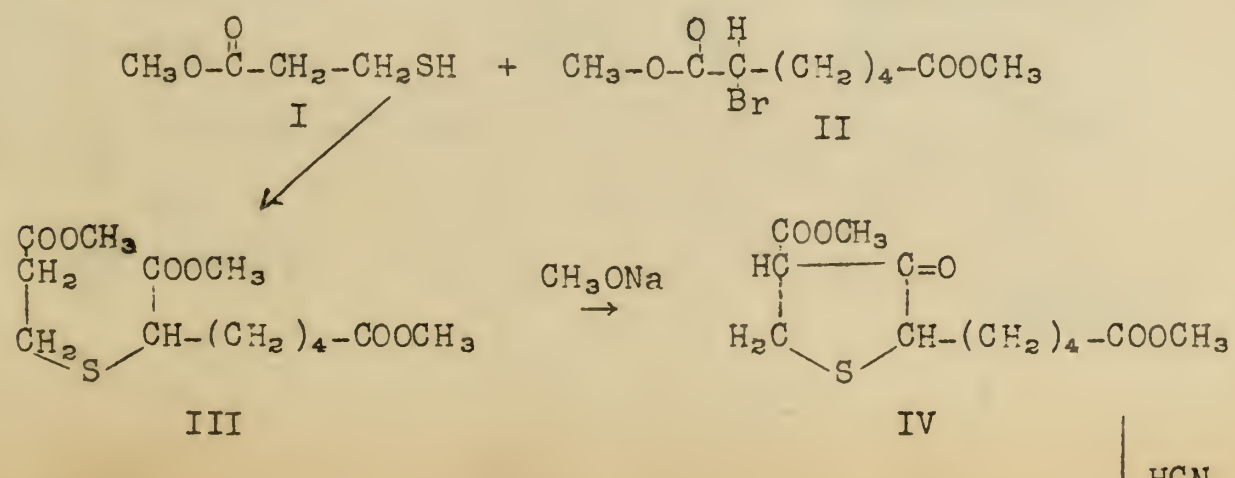
Synthesis of Grüssner and Coworkers.--A synthesis of biotin (8), based on earlier studies of Karrer and coworkers (9,10,11, 12,3), has recently been published by Grüssner and coworkers. This synthesis was carried out as follows:

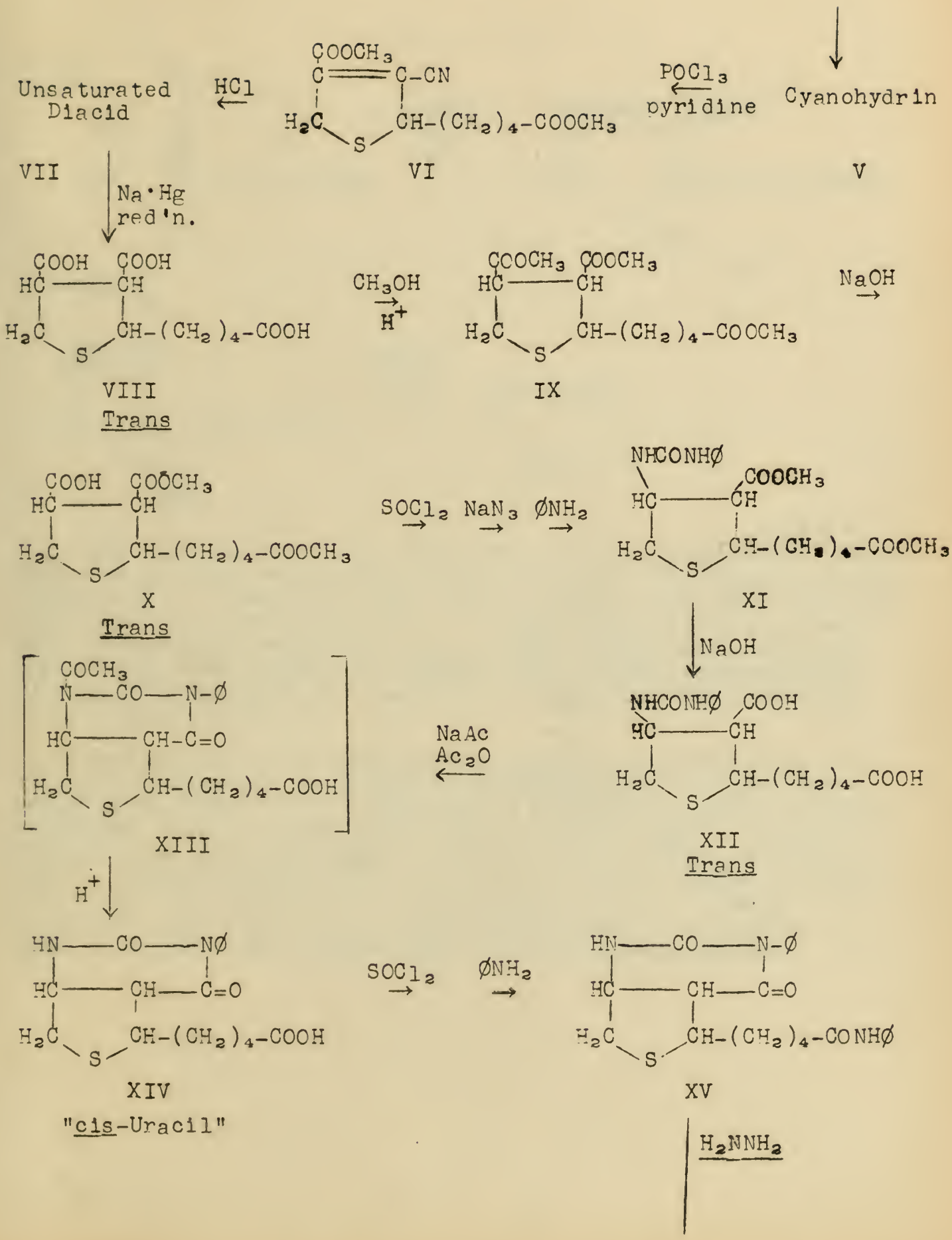


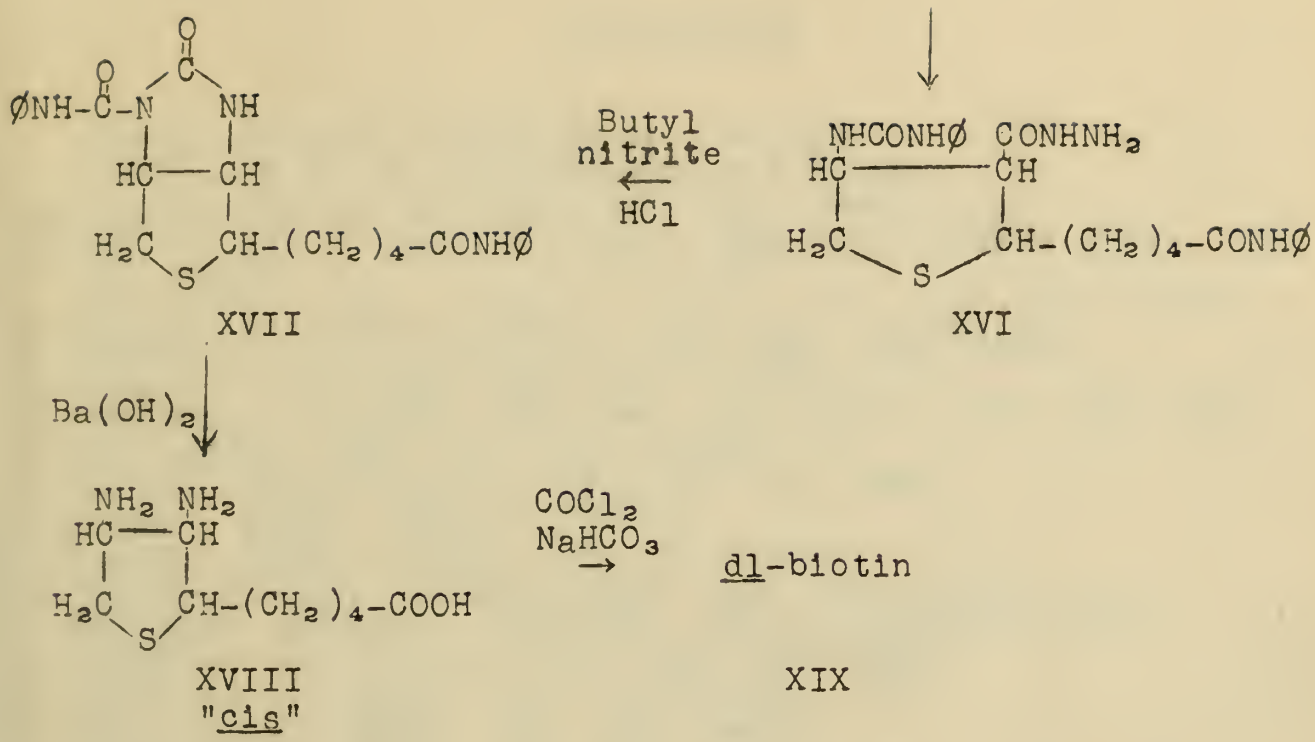


By appropriate separation of isomers these investigators obtained three racemic products (XIV) one of which was shown to be dl-biotin and two racemates which have been designated as dl-iso-ß-biotin and dl-Ψ-ß-biotin. These Swiss workers likewise did not obtain a fourth racemate from their synthetic procedure. The biotin isomers (dl-iso-ß-biotin and dl-Ψ-ß-biotin) did not correspond to the biotin isomers (dl-allobiotin and dl-epi-allobiotin) of the Merck group (13). Brown and coworkers (14) have suggested a possible explanation of the formation of these isomers on the basis of formation of thiophanium bromides in step XI with subsequent ring opening to an isomeric structure.

Synthesis of Baker and Coworkers.--A new synthesis of biotin has been published recently (15,16) by a method which "offers chemical control of isomers with no fractional crystallization being necessary to separate the isomers." The synthesis is as follows:




Unsaturated Diacid
HCl
VII
Na·Hg red'n.
VIII
Trans
VI
POCl3
pyridine
Cyanohydrin
V
CH3OH
H+
IX
NaOH
SOCl2
NaN3
ØNH2
X
Trans
XI
NaOH
XII
Trans
NaAc
Ac2O
XIII
H+
XIV
"cis-Uracil"
SOCl2
ØNH2
XV
H2NNH2



The configuration and structures of all questionable intermediates in this series have been proven and the final product, biotin XIX, is obtained without the necessity for separation of intermediate racemic mixtures. The cis uracil (XIV), on treatment with sodium methoxide, gave a trans hydrazide which was subsequently converted to a trans biotin isomer corresponding, by its melting point and degradation to dl-desthioallobiotin, to dl-epiallobiotin.

The synthesis of biologically inactive dl-epibiotin, the isomer not obtained by previous investigators, has now been reported by Baker (17). Employing a procedure similar to that described above for dl-biotin Baker has succeeded in preparing dl-epibiotin from the trans compound (VIII). Thus, starting with a single configuration in VIII "any one of three configurations related to biotin can be prepared at will, namely dl-biotin, dl-epibiotin and dl-epiallobiotin." No attempt was made to prepare the biologically inactive dl-allobiotin.

BIBLIOGRAPHY

1. Organic Seminar Abstract, Dec. 9, 1942.
2. duVigneaud et al, Science, 96, 455 (1942).
3. Organic Seminar Abstract, Dec. 13, 1944.
4. Kögl et al, Z. physiol. Chem., 279, 121 (1943); ibid., 279, 143 (1943).
5. Kögl et al, ibid., 281, 65 (1944); C.A., 39, 4614 (1945).
6. Harris et al, J. Am. Chem. Soc., 67, 2096 (1945).
7. Harris et al, ibid., 67, 2102 (1945).
8. Grüssner, Bourquin, Schnider, Helv. Chim. Acta, 28, 510, 517 (1945); ibid., 29, 770 (1946).
9. Karrer, Schmid, ibid., 27, 116, 124 (1944).
10. Schmid, ibid., 27, 127 (1944).
11. Karrer, Kehrer, ibid., 27, 142 (1944).
12. Karrer, Keller, Usteri, ibid., 27, 237 (1944).
13. Grüssner, Bourquin, Schnider, ibid., 29, 770 (1946).
14. Brown et al, J. Org. Chem., 12, 160 (1947).
15. Baker et al, ibid., 12, 167 (1947).
16. Baker et al, ibid., 12, 186 (1947).
17. Baker et al, ibid., 12, 322 (1947).

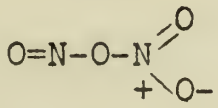
Reported by Frederick J. Pilgrim
May 2, 1947

THE ADDITION OF NITROGEN TETROXIDE TO OLEFINS

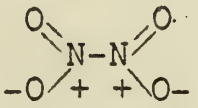
I. Nitrogen Tetroxide (N_2O_4).

N_2O_4 has long been regarded as an equilibrium mixture, $N_2O_4 \rightleftarrows 2NO_2$. The dimolecular form predominates at lower temperatures, while complete conversion to the monomolecular form occurs above 140°. N_2O_4 is a toxic gas; animals exposed to a concentration of one part per thousand die in a few minutes.

Infrared studies indicate that NO_2 is triangular in shape, $O^{\diagup N \diagdown}_{\diagdown + \diagup} O-$, while the structure of N_2O_4 has not been established clearly. X-ray analysis favors II, while chemical evidence rather favors I.



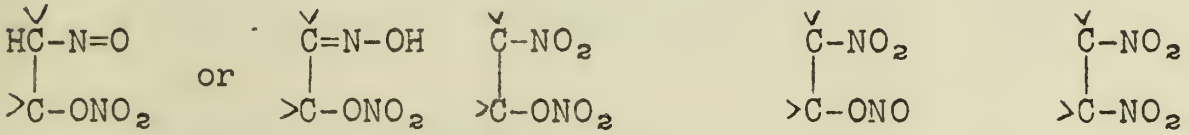
I



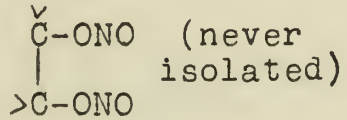
II

II. Work done to 1940.

A. The following possibilities have been suggested as ways in which >C=C< might add N_2O_4.



Nitrosonitrate or Nitronitrate Nironitrite Dinitro



Dinitrite

The earlier work is somewhat confused, due to the use of impure N_2O_4 and the formation of complicated, unstable products. Yields and experimental conditions are often not stated, and structures are based only on an analysis. Nomenclature varies from author to author.

B. Ethylene and simple ethylene derivatives.

Compound	Product	Reference
$CH_2=CH_2$	$CH_2(NO_2)-CH_2NO_2$	10
$CHX=CHX$	$CHX(NO_2)-CHXNO_2$	11, 12
$CI_2=CI_2$	Dinitro Deriv.	11, 12
$(CH_3)_2C=C(CH_3)_2$	Dinitro Deriv.	14
$Me_2-C=CH_2$	$\left[Me_2-C(ONO_2)-CH_2-C(=N-O)\right]_2$ 13%	14
	$Me_2-C=CH-NO_2$ 5-12%	
	$Me_2-C(NO_2)-CH_2-NO_2$ 12%	
	$Me_2-C(ONO)-CH_2-NO_2$ 18-23%	
$Me_2-C=CHCH_3$	$[Me_2-C(ONO_2)-CH(NO)CH_3]_2$ mainly	15
	$[Me-C(NO_2)-CH(NO)CH_3]_2$ 8-17%	
	Dinitro Deriv. 10-20%	
	$Me_2-C=C(NO_2)CH_3$ 10-20%	

C. Aryl ethylenes.

Most work done was carried out using N_2O_3, and gave rise to poorly characterized products. Stilbene yields the dinitro derivative.

D. Acetylenic compounds.

Compound	Product	Reference
$\phi-C\equiv CH$		18
$\phi-C\equiv C-\phi$	1,2-dinitro ethylene	18
$O-C\equiv CO_2C_2H_5$	compounds	19

E. Ethylenic acids.

The products are generally believed to be mixtures of the following types of compounds.

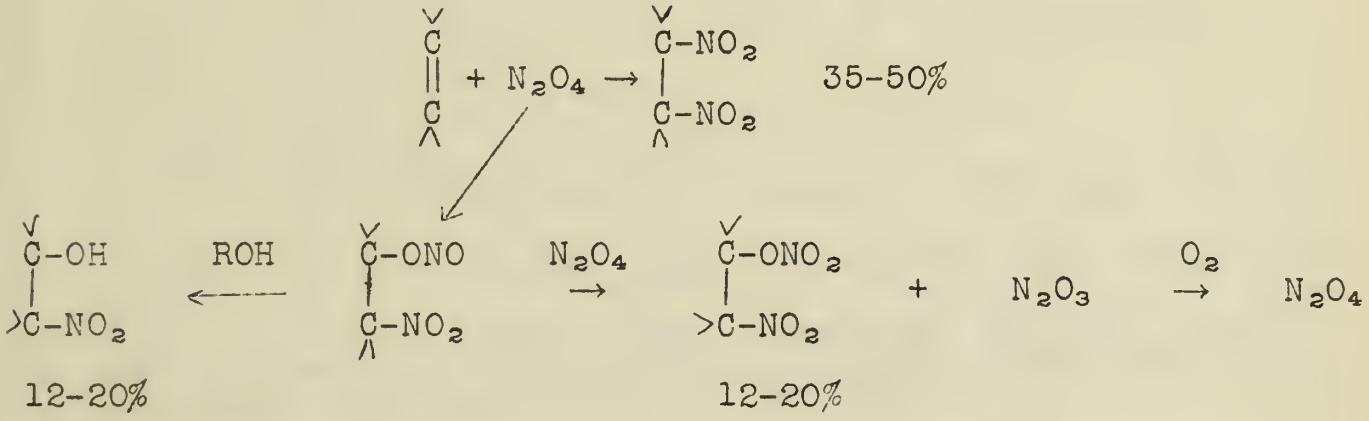
$$---C(NO_2)-C(NO_2)---CO_2H, \quad ---\underset{NO_2}{C}-\underset{ONO}{C}---CO_2H, \quad ---\underset{ONO}{C}-\underset{NO_2}{C}---CO_2H$$

F. Conjugated systems.

Compound	Product	Reference
$\phi-CH=CH-CH=CH-\phi$	$\phi-CH(NO_2)-CH=CH-CH(NO_2)-\phi$	20
$CH_2=C(\phi)-C(\phi)=CH_2$	1,2- and 1,4- addition of NO_2	21

III. Most Recent Work.

Levy and Scaife, by means of carefully controlled experiments using pure N_2O_4, have shown that dinitroparaffins, nitroalcohols, and nitroalkyl nitrates can be produced in good yields. The first products formed are a dinitroparaffin and an unstable nitronitrite which requires conversion to the nitroalcohol.



Effect of solvent.--The effect of a solvent is very marked, depending upon the olefin being used. In most cases the solvent is thought to moderate the oxidizing effect of N_2O_4.

Separation of products.--This great obstacle to the early workers has been overcome by special equipment for the removal of solvent and excess N_2O_4, and by the conversion of the unstable nitronitrites to nitroalcohols.

Mechanism.--A polar mechanism is suggested by the experimental results. Insufficient work has been done to postulate a complete mechanism.

Experimental.--Ethylene can be nitrated to give 70-80% of pure products. Liquid phase reaction has been found most satisfactory in all cases.

Propylene yields 75% of pure compounds. 1,2-Dinitropropane and β-nitroisopropyl nitrate, both new compounds, have been prepared and studied.

Bibliography

1. Lunge, Ber., 11, 1641 (1878).
2. Baker and Baker, J. Chem. Soc., 102, 2339 (1912).
3. Alexander, Z. angew. Chem., 24, 680 (1911).
4. Mellor, A Comprehensive Treatise on Inorganic and Theoretical Chemistry, Vol. 8, pp. 529-548. Longmans. Green and Company, London (1928).

5. Hendricks, Z. Physik., 70, 699 (1931).
6. Schaarschmidt and Hofmeier, Ber., 57, 32 (1924).
7. Schmidt, Ber., 34, 3536 (1901).
8. Wallach, Ann., 241, 315 (1887).
9. Wieland, Ann., 329, 225 (1903); 424, 71 (1921).
10. Semenoff, Jahreber., 1864, 480.
11. Blitz, Ber., 35, 1528 (1902); 30, 1201 (1897).
12. Burroughs and Hunter, J. Chem. Soc., 134, 1357 (1932).
13. Schmidt, Ber., 36, 2775 (1903).
14. Michael and Carlson, J. Org. Chem., 5, 1, 14 (1940).
15. Ibid., 4, 169 (1939).
16. Schmidt, German Patent 126,798.
17. Wieland and Blumick, Ann., 424, 100 (1921).
18. Wieland, Ber., 53, 1343 (1920).
19. Egoroff, Brit. Chem. Abstracts, 1903, I, 790; 1904, I, 216, 217.
20. Wieland and Stenzel, Ber., 40, 4825 (1907); Ann., 360, 290 (1908).
21. Allen, Elliot, and Bell, Chem. Abstracts, 33, 6284 (1939).
22. Levy and Scaife, J. Am. Chem. Soc., 1946, 1093, 1096, 1100.
24. Riebsomer, Chem. Rev., 36, 157 (1945).

Reported by E. W. Nommensen
May 9, 1947

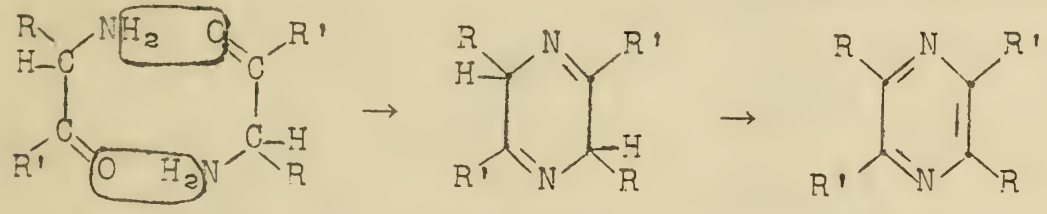
THE CHEMISTRY OF THE PYRAZINES

Until recent years the chemistry of pyrazine and its derivatives had received little attention in comparison with several other six-membered aromatic ring compounds. This was due mainly to the stability of the pyrazine ring to substitution reactions. Thus it was difficult to obtain the simple functional derivatives used as starting points in synthetic work. In the last decade discoveries of therapeutic properties of some pyrazine derivatives have stimulated interest in this subject; new preparations of the simple pyrazine derivatives have been devised and older methods have been improved.

I. Preparation of Pyrazine Derivatives.

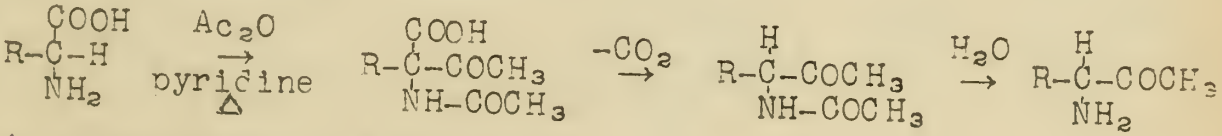
A. From α-amino carbonyl compounds.

When a free α-amino carbonyl compound is liberated from its stable salt by the action of a base, spontaneous condensation occurs resulting in a dihydro pyrazine. This is very readily oxidized to the corresponding pyrazine.



This method appears to be general for di- and tetra-substituted alkyl or aryl pyrazines. About the only limitation is the availability of the amino carbonyl compounds. Several methods of preparing these compounds follow:

1. Gabriels phthalimide synthesis using an α-bromo ketone.[1]
2. Action of acetic anhydride on α-amino acids.[2] The reaction proceeds as follows:



3. A rearrangement of oximes.

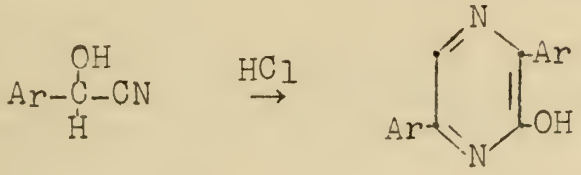
   Neber and cowrokers[3] found that treatment of oximes which contained an α-methylene group with p-toluene sulfonyl chloride in pyridine, followed by neutralization with a base produced dihydro pyrazine derivatives. Further investigations showed that α-amino ketones could be isolated from this reaction.
4. Reduction of iso-nitroso ketones.[4,5]

B. Preparation from 1,2-diamines and 1,2-diketones.[6]

This reaction has been applied to several combinations of diamines and diketones. A modification of this method[7] involves the use of HCN tetramer in place of the diamine. Several 2,3-dicyano pyrazines have been prepared in this way.

C. Preparation from cyanohydrins.[8]

When a pure aldehyde cyanohydrin is treated with HCl, a condensation takes place resulting in a disubstituted hydroxy pyrazine.

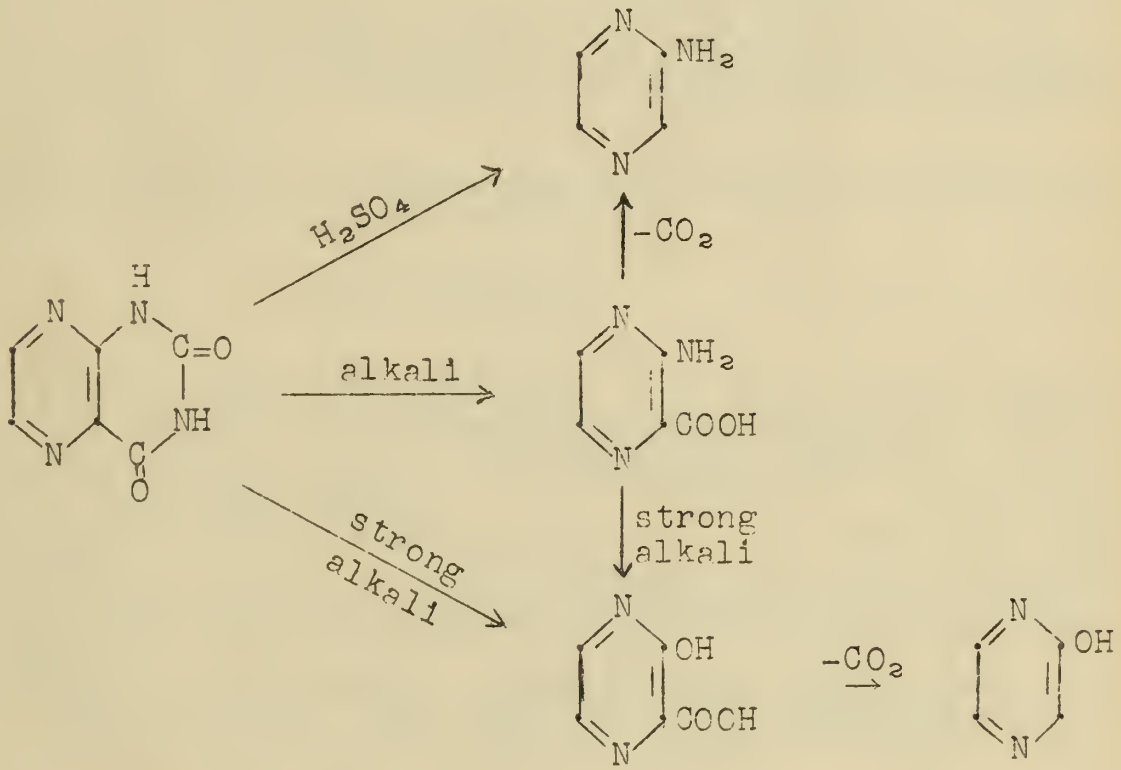


D. Preparation from lumazines.[9]

Amino pyrazine derivatives can be prepared in good yields by cleavage of lumazines with 80% H_2SO_4.

Alkaline cleavage produces 2-amino 3-pyrazinoic acids.

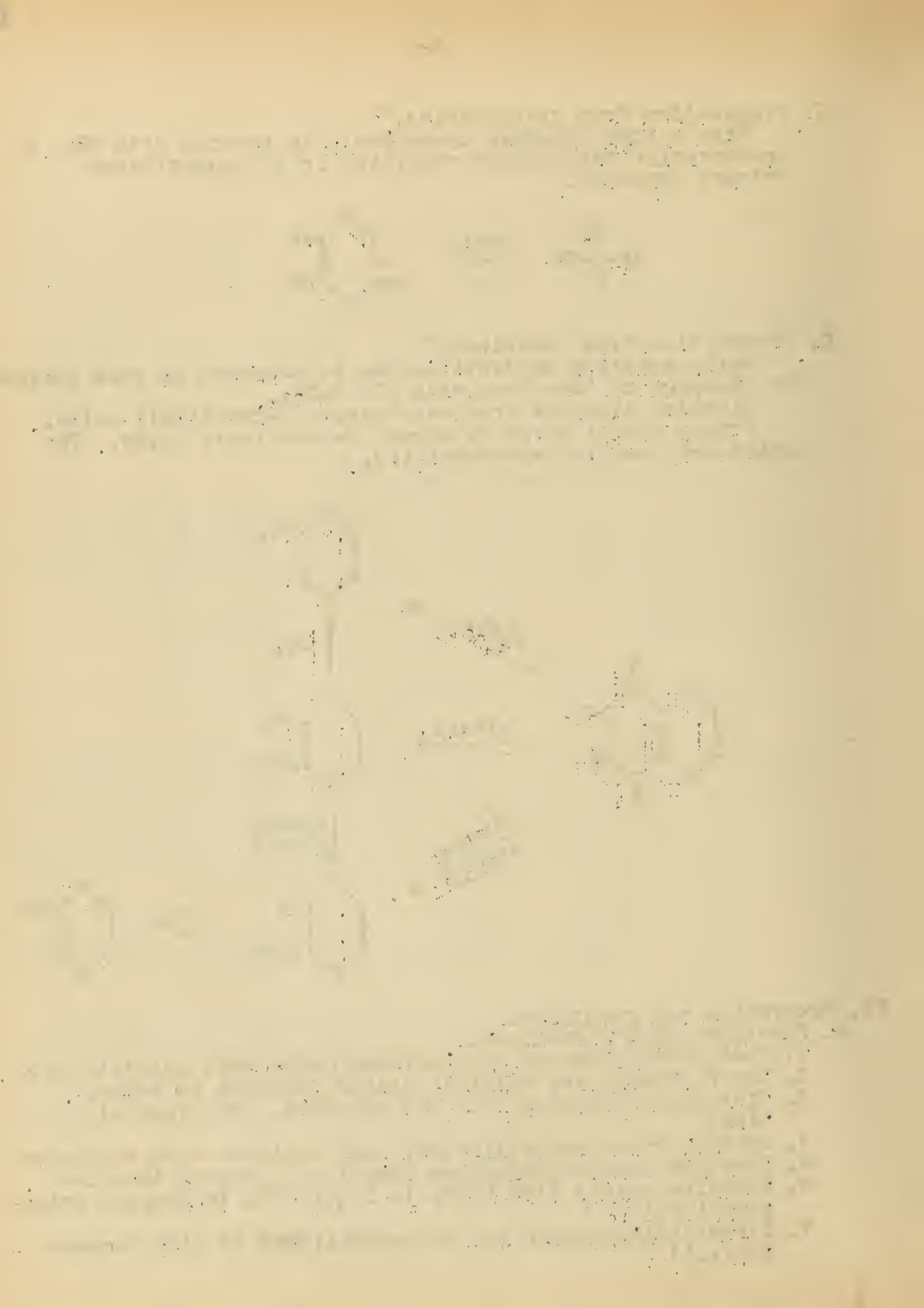
Strong alkali gives 2-hydroxy 3-pyrazinoic acids. The acids are readily decarboxylated.



II. Properties and reactions.

A. Pyrazine and its homologs.

1. Weak bases decreasing in strength with aryl substituents.
2. Lower members are volatile solids, soluble in water.
3. Side chains readily oxidized to acids, one group at a time.
4. Methyl groups are activated; they condense with aldehydes.
5. Pyrazine nucleus resembles pyridine -- highly inactive.
6. Pyrazine reacts with $NaNH_2$ in liquid NH_3 to produce amino-pyrazine.[10]
7. Direct halogenation can be accomplished at high temperatures.[11]



B. Acid derivatives
   1. The Hofmann degradation can be used to prepare amino compounds in good yields but the Curtius reaction fails[12] since the isocyanate is too stable to hydrolysis.
   2. Pyrazine 2,3-dicarboxyamide with excess NaOBr rearranges to yield lumazine but one mol of NaOBr produces the amino acid.[13]

C. Amino derivatives.[14]
   Can be successfully diazotized only with nitrosyl sulfuric acid. The diazonium salts can be hydrolyzed to hydroxy compounds and can also be converted to pyrazyl halides.

D. Hydroxy derivatives.
   1. They exist mainly as "Pyrazones."
   2. They are amphoteric.
   3. They couple with diazonium salts to yield azo derivatives.[15]

III. Uses of some pyrazine derivatives.

A. Sulfapyrazine
   This sulfa drug was found to be very effective in pneumococcal[16] and β-hemolytic streptoccocal[17] infections. Its advantages are slow absorption and excretion in the body.

B. Pyrazine mono- and dicarboxylic acids were found to possess anti-pellagra activity without the vasodilator effect of nicotinic acid.[18]

C. Several substituted carboxyamides and hydrazides have been prepared for use an analeptics.[19]

BIBLIOGRAPHY

1. S. Gabriel, Ber., 41, 1127 (1908).
2. H. Dakin and R. West, J. Biol. Chem., 78, 751 and 757 (1928); Levene and Steiger, J. Biol. Chem., 79, 95 (1928).
3. Neber et. al, Annalen, 449, 109 (1926); 467, 52 (1928); 493, 281 (1932); 515, 283 (1935).
4. Hartung, Munch, Deckert, and Crossley, J. Am. Chem. Soc., 52, 3317 (1930).
5. Tiffeneau, Levy, and Ditz, Bull. soc. chim., 2, 1848 (1935).
6. Gabriel and Sonn, Ber., 40, 4850 (1907); Böttcher, Ber., 46, 3084 (1913).
7. Hinkel, Richards, and Thomas, J. Chem. Soc., 1937, 1432.
8. Japp and Knox, J. Chem. Soc., 87, 701 (1905); McCombie and Parry, J. Chem. Soc., 95, 584 (1909); Ingham, J. Chem. Soc., 1927, 692.
9. Weijlard, Tishler and Erickson, J. Am. Chem. Soc., 67, 808 (1945); Ellingson, Henry and McDonald, J. Am. Chem. Soc., 67, 1711 (1945).
10. Crossley and English, U.S.P. 2,394,963; C.A. 40, 3143 (1946).
11. P. S. Winnek, U.S.P. 2,396,066; C.A., 40, 3143 (1946); Dixon and Sayward, U.S.P. 2,403,710; C.A., 40, 6103 (1946).
12. Spoerri and Erickson, J. Am. Chem. Soc., 60, 400 (1938).
13. Baxter and Spring, J. Chem. Soc., 1945, 220.
14. Erickson and Spoerri, J. Am. Chem. Soc., 68, 400 (1946).
15. Gastaldi and Principalle, Gazz. chim. ital., 58, 679 (1928).
16. Ruegsegger et. al, J. Pharmacol., 73, 468 (1941); Am. J. Med. Sci., 202, 432 (1941); 204, 186 (1942).
17. Schmidt and Seeler, J. Pharmacol., 77, 277 (1944).
18. Bean and Spies, Southern Med. J., 32, 793 (1939); Am. Heart J., 20, 62 (1940).
19. F. E. Merck, Ger. 632,257; C.A., 30, 6894 (1936).

Reported by R. P. Seven
May 9, 1947

THE DUFF REACTION

In a series of papers (1) (2) (3) (4), Duff described a general method for the synthesis of ortho formyl phenols and para dialkylaminobenzaldehydes, in which a phenol or dialkylaniline is reacted with hexamethylenetetramine.

The mechanism, as proposed by Duff, is as follows.

1. $3C_6H_5OH + (CH_2)_6N_4 \rightarrow 3\ o\text{-}HOC_6H_4CH_2N{=}CH_2 + NH_3$

2. $o\text{-}HOC_6H_4CH_2N{=}CH_2 \rightarrow o\text{-}HOC_6H_4CH{=}NCH_3$

3. $o\text{-}HOC_6H_4CH{=}NCH_3 + H_2O \rightarrow o\text{-}HOC_6H_4CHO + CH_3NH_2$

This is similar to the reaction mechanism proposed by Sommelet (5) to explain the conversion of benzyl chloride by hexamethylene tetramine to benzaldehyde. Graymore and Davies (6) have verified steps 2 and 3.

Several procedures have been employed.

A. Reference (1) in aqueous solution
B. Reference (2) in glacial acetic acid
C. Reference (3) Duff's general procedure in glyceroboric acid
D. Reference (7) Liggett and Diehl modified procedure
E. Reference (4) acetic-formic acid mixture for dialkylanilines

The only other general method for the direct introduction of a formyl group o to a phenolic hydroxyl group is the Reimer-Tiemann reaction. The Duff reaction appears to be of somewhat greater applicability. The advantages are complete synthesis in 2-3 hours, no unreacted phenol present, no bisulfite extraction required, and the ortho substituted product is usually obtained in practically pure condition by steam distillation. The main disadvantage as an aldehyde synthesis is the low yields obtained.

Bibliography

1. Duff and Bills, J. Chem. Soc., 1987 (1932).
2. Duff and Bills, ibid., 1305 (1934).
3. Duff, ibid., 547 (1941).
4. Duff, ibid., 276 (1945).
5. Sommelet, Compt. Rend., 157, 854 (1913).
6. Graymore and Davies, J. Chem. Soc., 293 (1945).
7. Liggett and Diehl, Proc. Iowa Acad. Sci., 52, 191 (1945).

Reported by R. G. Beaman
May 9, 1947

COMPCUNDS SUBJECTED TO THE DUFF REACTION

Phenol OH=1	Salicylaldehyde CHO=1	Yield	Method
phenol	salicylaldehyde	12%	C
2-Me	3-Me	14	C
2-Me	3-Me 5-CHO	3.8	C
3-Me	4-Me	16	C
4-Me	5-Me	27	C
4-Me	5-Me	29	D
4-Et	5-Et	18	D
2-Me 4-Me	3-Me 5-Me	32	D
2-Me 5-Me	3-Me 6-Me	29	D
2-Me 5-Me	3-Me 5-CHO 6-Me(?)	small	D
3-Me 4-Me	4-Me 5-Me(?)	45	D
3-Me 5-Me	4-Me 6-Me	16	C
2-iPr 5-Me	3-iPr 6-Me	17	C
2-iPr 5-Me	3-iPr 6-Me	16	D
2-Me 5-iPr	3-Me 6-iPr	25	C
3-Me 4-tBu	4-Me 5-tBu(?)	14	D
4-tBu	5-tBu	22.5	C(a)
2-tAm	3-tAm	11	D
2-Me 4-tAm	3-Me 5-tAm	19	D
2-Cl	3-Cl	7	C
4-Cl	5-Cl	11	C
2-Br	3-Br	14.5	D
2-Cl 4-Cl	3-Cl 5-Cl	7	C
2-Br 4-Br	3-Br 5-Br	6.8	D
3-Me 4-Cl	4-Cl 5-Me	8	C
3-Me 4-Cl	5-Cl 6-Me(?)	30	D
3-Me 4-Cl	3-CHO 5-Cl 6-Me	14	C
3-Me 4-Cl 5-Me	4-Me 5-Cl 6-Me	27	C
2-iPr 4-Cl 5-Me	3-iPr 5-Cl 6-Me	10	D
2-Cl 4-tBu	3-Cl 5-tBu	29	D
2-Br 4-tBu	3-Bu 5-tBu	22	C

Phenol OH=1	Salicylaldehyde CHO=1	Yield	Method
3-OH		resin	C(b)
3-OH 5-OH		resin	C(b)
2-OH 4-tBu	3-OH 4-tBu(?)	26	D
2-nBuO	3-nBuO	15	D
2-COOH	3-COOH	7.5	A
2-COOH	3-COOH	9	B
2-COOH	product was 3-CCOH 4-OH benzaldehyde	15	A
2-COOH	product was 3-CCOH 4-OH benzaldehyde	17	B
3-CCOH	complex amorphous products		A
4-CCOH	complex amorphous products		A
2-$NO_2$4-NO_2		0	D
2-Me 3-NO_2 5-NO_2		0	D
2-Ph		0	D
4-Ph	5-Ph	23	C
4-Ph	5-Ph	good	D

Compound	Product	Yield	Method
α-naphthol		0	B
β-naphthol	Schiff's Base	quant.	B
β-naphthol	2-OH naphthaldehyde	27	C
2-CH pyridine		0	D
"hydroxypyridines"		0	C(b)
"hydroxyquinolines"		0	C(b)
thiophenol		0	D
$Me_2NC_6H_5$	paraCHO	38	E
$Et_2NC_6H_5$	paraCHO	30	E
$MeEtNC_6H_5$	paraCHO	33	E
$BenzylMeNC_6H_5$	paraCHO	44	E
$BenzylEtNC_6H_5$	paraCHO	36	E
2-$MeMe_2NC_6H_4$		0	E
3-$MeMe_2NC_6H_4$	paraCHO	17	E
4-$MeMe_2NC_6H_4$		0	E

(a) J. B. Ziegler, private communication.
(b) Mentioned without details; Ferguson, Chem. Rev., 38, 227 (1946).

THE USE OF SULFURYL CHLORIDE IN SYNTHESIS

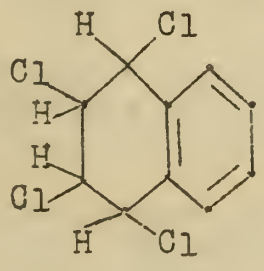
Sulfuryl chloride is a versatile reagent with great potentialities in synthetic organic chemistry. It may be used with an amazing degree of control for the chlorination or sulfonation of both aromatic and aliphatic derivatives; it serves also for the preparation of esters of chlorosulfonic acid from alcohols, sulfamides from secondary amides and acid chlorides and anhydrides from sodium salts of acids. Recently several articles have appeared describing its use in widely differing syntheses.

I. Chlorination

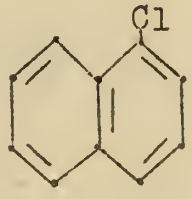
A. Aromatic Compounds.--Nuclear substitution of activated ring compounds occurs readily, is easily controlled, and takes place without catalysts in the case of phenols, amines, certain heterocyclics and polynuclear hydrocarbons (1). Mono-, di- or tri-chlororesorcinol, and mono- or di-chloroanthranilic acid are examples of stepwise chlorination (1). Indole gives 2-chloro, or 2,3-dichloroindole, depending upon the amount of SO_2Cl_2 used (1). Pyridine oxide reacts with SO_2Cl_2 in a sealed tube at 120°C. to give the α-chloro and γ-chloro compounds (2).

The sensitivity of SO_2Cl_2 as a chlorinating agent to changes in the experimental conditions is illustrated by its reported action on naphthalene (1). The following products are obtained:

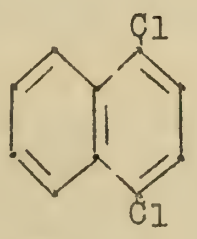
With 2 SO_2Cl_2 at 80°



With SO_2Cl_2 and $AlCl_3$ at 25°



at 100-140°C with 2 SO_2Cl_2



2. Nuclear substitution of unactivated aromatic types is catalyzed by halogen carriers. A mixture of $AlCl_3$ and S_2Cl_2 in a 1% concentration in SO_2Cl_2 gives rapid, easily controlled, stepwise chlorination at low temperatures; for example, stepwise polychlorination through the hexachloro derivative occurs with benzene, and toluene yields the monochloro through the pentachloro compound without cleaving or attacking the side chain (1).

B. Aliphatic and Aliphatic-Aromatic Compounds. 1. Selective side chain chlorination yielding the α-chloro derivative exclusively occurs when a trace of peroxide is used with m-xylene and SO_2Cl_2 (1). The α-chloro compounds are also obtained from p-chlorotoluene, ethyl benzene and in 90% yield from isopropyl benzene. t-Butyl benzene gives substitution readily on the β-carbon (1).

2. Less than one mole per cent of peroxide also promotes rapid substitution in simple aliphatic compounds in the dark at low temperatures. Products obtained are those expected from ordinary photochemical chlorination. Thus n-heptane gives with SO_2Cl_2 and peroxide 15% of primary and 85% of secondary chlorides; 1-chlorobutane is substituted only slightly in the 1-position, 25% in the 2-, 50% in the 3-, and 25% in the 4-position (1). Neither chloroform nor sym-tetrachloroethane is further chlorinated by this method (1).

3. Addition of chlorine to olefins is also catalyzed by peroxide, giving the saturated dichloro compound and SO_2 (1).

4. α-Chloro acids above acetic acid are best prepared, according to recent reports (1,3,4) using SO_2Cl_2 alone or with iodine as catalyst in a refluxing ether solution of the acid. A yield of 98% is reported by Gulat (3) in the case of $C_6H_5CONHCH_2CH_2CH_2CH_2CHClCOOH$. Guest (4) prepared several acids of the type $RCHClCOOH$, where R equals C_4H_9-, C_6H_{13}-, C_7H_{15}-, $C_{12}H_{25}$-, $C_{16}H_{33}$- using this method.

If peroxide is present substitution takes place on the β- and γ-positions as well, so that a mixture of the α-, β-, and γ-chloro isomers results (1).

5. Silanes are readily chlorinated using SO_2Cl_2 and peroxide catalyst. Whitmore (5) has prepared several of these compounds -- for example, α-chloroethyl trichlorosilane and α-chlorobenzyl trichlorosilane.

6. Aldehydes and ketones without an α-hydrogen are chlorinated in the usual way by SO_2Cl_2 and peroxide; for example, benzaldehyde gives benzoyl chloride. With an α-hydrogen present substitution in this position occurs without catalyst at room temperature, probably by way of an enol form (1).

II. Sulfonation

A. Aromatic Compounds.--Töhl and Eberhard (6) have prepared the sulfonyl chloride derivatives of benzene, toluene, the xylenes and of mesitylene, etc. The hydrocarbon and sulfuryl chloride are cooled and small amounts of $AlCl_3$ dropped in.

B. Aliphatic Compounds.--Pyridine and light induce rapid sulfonation of many aliphatic compounds by SO_2Cl_2 to give alkyl sulfonyl chlorides. The yields are good, reaching 70% (1). Among the compounds sulfonated are n-butane, ethyl benzene, t-butyl benzene and cyclohexane.

With lower aliphatic acids no catalyst is needed; the sulfonation proceeds smoothly to give a new type of compound -- the inner anhydride of the sulfocarboxylic acid (7).

$$\begin{matrix} CH_2\text{-}COOH \\ | \\ CH_3 \end{matrix} \xrightarrow[\text{light, } 50^\circ]{SO_2Cl_2} \left[\begin{matrix} CH_2\text{-}COOH \\ | \\ CH_2SO_2Cl \end{matrix}\right] \xrightarrow[\text{cond.}]{\text{anhyd.}} \begin{matrix} CH_2\text{-}C(=O)\text{-}O \\ | \\ CH_2\text{-}SO_2 \end{matrix} \quad 52\%$$

This product is accompanied by a 45% yield of α-chloro acid. Higher aliphatic acids give good yields of mixtures of β- and γ-sulfonated isomers (7).

III. Miscellaneous.

A. Sulfuryl chloride reacts as an acid chloride of sulfuric acid. Alcohols give compounds of the type $ROSO_2Cl$, and with an excess of alcohol $(RO)_2SO_2$ (1). Aliphatic secondary amines undergo similar reactions; from the amine itself and SO_2Cl_2 is obtained $R_2NSO_2NR_2$, while the amine hydrochlorides are not so reactive, giving the monosulfamide, R_2NSO_2Cl. Aniline itself gives sulfanilide, $C_6H_4NHSO_2Cl$, in a 60% yield when SO_2Cl_2 in dry ether is dropped into a cooled solution of the amine in three times its volume of dry ether. p-Toluidine undergoes a similar reaction (8).

2. An interesting use of SO_2Cl_2 in acylation reactions is made by using the addition compound with pyridine which reacts with alcohols and acids to give the alkyl and acyl chlorides, respectively (1). If a phenol or amine is present it is acylated; for example, benzanilide is obtained from aniline and benzoic acid.

3. By the action of SO_2Cl_2 on the sodium salts of organic acids, acid chlorides and acid anhydrides are formed (1). This has found application in the preparation of benzoyl chloride and benzoic anhydride, and in the manufacture of acetic anhydride (1).

BIBLIOGRAPHY

1. Brown, H. C., Ind. Eng. Chem., 36, part 2, 785 (1944). (This article has a list of 78 references following it).
2. Bobrauski, B., Kochanska, L., and Kowalewska, A., Ber., 71, 2385 (1938).
3. Gulat, A., J. Am. Chem. Soc., 69, 86 (1947).
4. Guest, H. H., ibid., 300 (1947).
5. Whitmore, F. C., ibid., 68, 486 (1946).
6. Tohl, A., and Eberhard, O., Ber., 26, 2940 (1893).
7. Kharasch, M. S., Chao, T. H., and Brown, H. C., J. Am. Chem. Soc., 62, 2393 (1940).
8. Wohl, A., and Koch, F., Ber., 43, 3295 (1910).

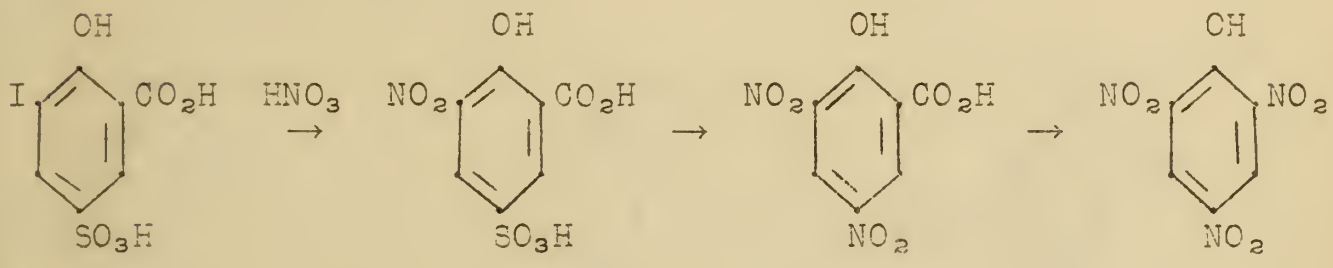
Reported by Neal O. Brace
May 16, 1947

ANOMALOUS NITRATION REACTIONS

In many instances of aromatic nitration not only hydrogen atoms, but halogens, alkyl, alkoxyl, acyl, carboxyl and sulfonic groups can be replaced by nitro groups. This is true especially in phenols and their ethers, in which replacement of various atoms or groups ortho or para to -OH or -OR occurs more or less readily, the ease of displacement decreasing roughly in the following order:

$$H > I > SO_3H > CO_2H > COR > Br > Cl$$

This is illustrated by the following example:[1]

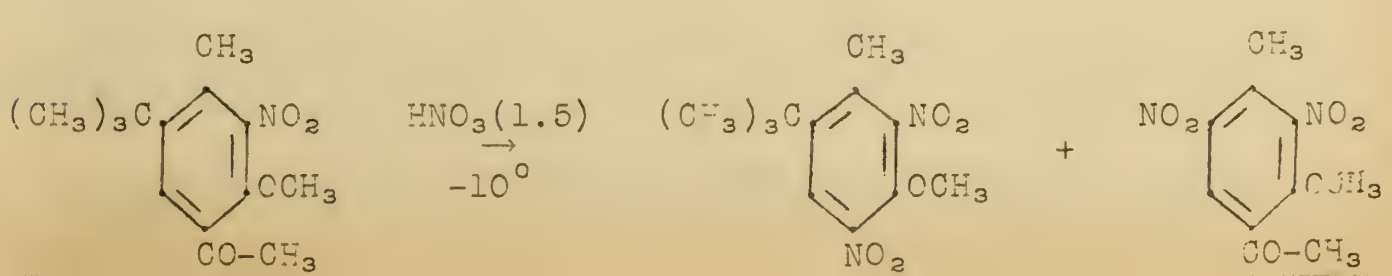


The tendency of aromatic compounds to undergo anomalous nitration increases in general with the number of substituents.

Polyalkylbenzenes.--Replacement of alkyl groups is general in penta- and hexaalkylbenzenes; from less substituted rings only branched side chains are removed.

Cymene[2,3] can be made to yield a great number of products by varying the composition of the nitrating mixture and the temperature: mixed acids favor the formation of normal nitration products (2-nitrocymene; 2,6-dinitrocymene) and of replacement products (p-nitrotoluene; 2,4-dinitrotoluene; trinitrotoluene), whereas with nitric acid alone oxidation products (methyl p-tolyl ketone, p-toluic acid and nitrotoluic acids) are obtained.

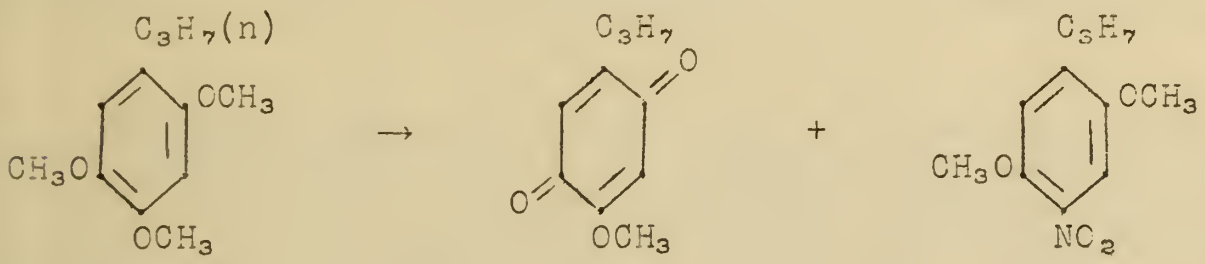
Penta- and hexamethylbenzene give dinitroprehnitene (o-dinitrotetramethylbenzene) with acs. HNO_3 in H_2SO_4 and $CHCl_3$ at low temperature, whereas the corresponding ethyl compounds yield p-dinitrotetraethylbenzene.[4,5] These are two of the three only known exceptions to Barbier's rule[6] which states that in the stepwise nitration of a highly substituted benzene ring a second nitro group replaces always a substituent meta to the first entering nitro group. This rule can be illustrated by the following reaction:



In the nitration of polymethylbromobenzenes, a methyl group is sometimes transformed into $-CH_2ONO_2$ (nitrate formation).[7] Bromopentamethylbenzene yields 4-bromo-5,6-dinitrohemimellitene with mixed acids, but the nitrates of isomeric bromotetramethylbenzyl alcohols with fuming HNO_3 alone; treatment of these nitrates with sulfuric acid transforms the $-CH_2ONO_2$ group into a nitro group.[8]

Phenols and Phenolic Ethers.--Replacement of isopropyl and tertiary butyl groups has been observed by a number of workers. Thus thymol yields with mixed acids 2,4,6-trinitro-m-cresol.[9] 3-Methyl-4-t-butylanisole yields, in addition to the normal nitration product, 3-methyl-4,6-dinitroanisole.[10]

Quinone formation or replacement of alkoxyl groups may occur in some polyphenolic ethers.



Fuming HNO_3 at low temperature favors formation of the quinone at 50° with dilute HNO_3 in glacial acetic acid the main product is the compound in which one methoxyl has been replaced by a nitro group.

Halogenated Phenols and Phenolic Ethers.--Halogens ortho or para to a hydroxyl or alkoxyl group are more or less easily replaced (I > Br > Cl). In some cases the halogen replaced migrates to another position in the ring; thus the nitration of 4-iodoanisol yields 2-iodo-4-nitroanisole.[12]

Sometimes quinone formation occurs; thus 4-fluoro-2,6-dibromoanisole yields 2,6-dibromo-p-benzoquinone.[13]

Phenolic Acids, Aldehydes and Ketones[14,15,16].--A carboxyl group is more readily replaced than an aldehyde group, which in turn is more easily replaced than an aceto group. Thus 2,4-dinitroanisole and 2,4,6-trinitroanisole are the main products in the nitration of p-methoxybenzoic (anisic) acid; only a minor quantity of trinitroanisole is obtained in the nitration of p-methoxybenzaldehyde (anisaldehyde); p-methoxyacetophenone yields only normal nitration products.

If more than one alkoxyl group is present the displacement reaction occurs much more readily; thus 3,4-dimethoxyacetophenone is completely transformed into 1,2-dinitro-4,5-dimethoxybenzene.

Cinnamic Acids[17].--Action of fuming HNO_3 (sp. gr. 1.50) at 0° on cinnamic acid yields a mixture of o- and p-nitrocinnamic acids,

but with absolute nitric acid (sp. gr. 1.52) a mixture of β-2- and β-4-dinitrostyrene is obtained.

$$C_6H_5CH{=}CHCO_2H \xrightarrow[(1.50)]{HNO_3} NO_2C_6H_4CH{=}CHCO_2H \xrightarrow[(1.52)]{HNO_3} NO_2C_6H_4CH{=}CH{-}NO_2$$

Nitration of ethyl p-nitrocinnamate with abs. HNO_3 at 0° yields a nitrate which can be isolated, but in the presence of water loses rapidly nitric acid to yield a mixture of the cis- and trans-α-nitro-β-(p-nitrophenyl)acrylic esters.

$$NO_2C_6H_4CH{=}CHCO_2Et \xrightarrow{HNO_3} NO_2C_6H_4\underset{CNO_2}{CH}{-}CH\begin{matrix}CO_2Et\\NO_2\end{matrix} \xrightarrow{H_2O} NO_2C_6H_4CH{=}C\begin{matrix}CO_2Et\\NO_2\end{matrix}$$

Sulfonic Acids.--In the nitration of phenolsulfonic acids, the sulfo group is unaffected if it is meta to the hydroxyl, in the other cases at least one position ortho or para to the hydroxyl is nitrated, if free, before the sulfo group is removed.[1] An important application is the manufacture of picric acid by the sulfonation and subsequent nitration of phenol.

The sulfo group is replaced with a comparable ease in naphtylaminesulfonic acids and the ethers of naphtolsulfonic acids. There are also a few cases where a sulfo group is replaced in polyalkylbenzenesulfonic acids; thus m-xylene-4-sulfonic acid yields some trinitroxylene under very strenuous conditions.[18]

Sulfo groups are replaced much more easily by nitro groups when nitrous fumes are passed through an aqueous solution of the acid.[19] By this procedure p-chlorobenzenesulfonic acid yields p-chloronitrobenzene. In m-aminobenzenesulfonic acid the nitrous fumes cause first diazotization and hydrolysis of the amino group; then 3,6-dinitrophenol is formed by the very unusual replacement of a sulfo group meta to a hydroxyl.[20]

Numerous further examples of replacement of sulfo groups by nitro groups are listed in Suter's Organic Chemistry of Sulfur.[1] The general subject of anomalous nitrations has recently been reviewed very exhaustively by Nightingale.[21]

Bibliography

1. Suter, "Organic Chemistry of Sulfur", Wiley, New York, 1944, p. 406ff.
2. Alfthan, Ber., 53, 78 (1920).
3. Kobe and Doumani, Ind. Eng. Chem., 31, 257 (1939).
4. Smith and Harris, J. Am. Chem. Soc., 57, 1289 (1935).
5. Smith and Guss, J. Am. Chem. Soc., 62, 2635 (1940).
6. Barbier, Helv. Chim. Acta, 11, 157 (1928).
7. Rinkes, Rec. trav. chim., 58, 538 (1939).
8. Smith and Horner, J. Am. Chem. Soc., 62, 1349 (1940).
9. Armstrong and Rennie, Chem. News, 47, 115 (1883).
10. Darzens and Levy, Compt. rend., 193, 321 (1931).
11. Thoms, Ber., 36, 854, 1715 (1903).
12. Robinson, J. Chem. Soc., 109, 1078 (1916).
13. Hodgson and Nixon, J. Chem. Soc., 1930, 1085.
14. Salway, J. Chem. Soc., 95, 1155 (1909).
15. DeLange, Rec. trav. chim., 45, 19 (1926).
16. Harding, J. Chem. Soc., 105, 2790 (1914).
17. Van Der Lee, Rec. trav. chim., 45, 674 (1926).
18. Karslake and Morgan, J. Am. Chem. Soc., 30, 828 (1908).
19. Datta and Varma, J. Am. Chem. Soc., 41, 2039 (1919).
20. Datta and Varma, J. Indian Chem. Soc., 4, 321 (1927).
21. Nightingale, Chem. Rev., 40, 117 (1947).

Reported by Anthony W. Schrecker
May 16, 1947

STRAINLESS CYCLOHEXANE RINGS

I. Baeyer Strain Theory and the Sachse-Mohr Hypothesis.--According to the Baeyer Strain Theory, all carbocycles are planar and the molecules are consequently strained in proportion to the amount of deviation from the tetrahedral bond angle. The stability of a ring will decrease with increasing distortion of the bond angles. This theory accounts for much of the experimental data relating to rings smaller than six members but fails to explain the behavior of larger-sized rings. Sachse pointed out that strain in the Baeyer sense can be eliminated from a structure having more than five carbon atoms in the ring if the ring is non-planar. Two such strain-free configurations are possible in the case of cyclohexane. Such multiplanar structures which involve no distortion of the tetrahedral bond angles are termed "strainless rings." This conception was developed by Mohr, who postulated that the energy involved in the conversion of one of Sachse's strain-free configurations into another is so small that forces due to molecular collisions can overcome it.

II. Theoretically Possible Isomers in Substituted Cyclohexanes.--Cyclohexane can exist in two forms, a "boat" or "C" form and a "chair" or "Z" form. The "boat" form is flexible because of relative strain-free rotation of its atoms. Because of its mobility, all the hydrogens are equivalent in the "boat" form and it is sterochemically indistinguishable from a planar ring. The "chair" form, however, is a rigid structure. Considerable distortion is necessary to interconvert the "C" and "Z" forms.

On the basis of this information, the number of isomers in various substituted cyclohexanes can be predicted (1). Some typical examples are: $C_6H_{11}a$, 2Z, 1C; $C_6H_{10}ab$, 2Z, 1C; $a_2C_6H_8b_2$, 1Z, 1C; $a_2C_6H_8bc$, 2Z, 1C; abC_6H_8cd, 4Z, 2C.

III. Physical Evidence.--X-ray, infrared, dipole moment, and Raman spectra data indicate a multiplanar structure of cyclohexane with probably an equilibrium mixture present (2,3,4).

IV. Chemical Evidence.--The existence of "boat" and "chair" isomers would be possible if the substituents were of such a nature as to stabilize the positions of the atoms in the ring by preventing intramolecular rotation. Such a situation is known to occur in fused ring systems, such as decalin, where the cis-trans isomerism is definite evidence for the strainless configurations containing five or more atoms. Numerous attempts to find substituents which will stabilize the two forms in the monocyclic compounds have been reported.

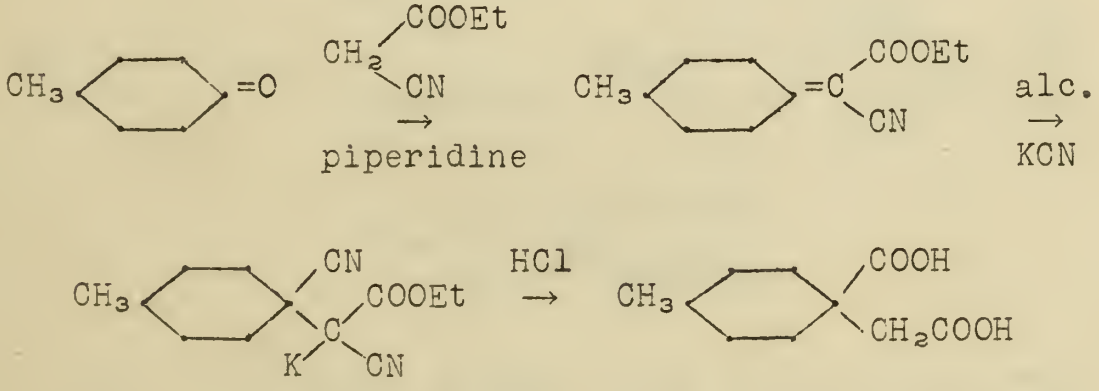
Schrauth and Görig (5) claim to have prepared three different forms of dicyclohexyl, (A) b.p. 235-237°, (B) 227-228°, (C) 219.5-221.5° Dehydration of p-cyclohexylcyclohexanol followed by hydrogenation gives form B. o-Cyclohexylphenol on hydrogenation to the cyclohexanol and subsequent dehydration, gives a cyclohexene which yields predominantly A or C depending on the conditions of its hydrogenation. A is stable, while the other two are transformed

into mixtures of the three by the action of aluminum chloride or light. Kursanoff (6), by condensation of cyclohexyl iodide, obtained a product of b.p. 234-236°, while Wallach (7), by condensing cyclohexanone with itself and reducing the product, obtained a dicyclohexyl, b.p. 227°. The purity of these products has not been established.

According to Vogel (9), methylcyclohexanes can be isolated in "C" and "Z" forms depending on the method of preparation. He obtained a single stable methylcyclohexane by the Clemmensen reduction of pure 2-, 3-, or 4-methylcyclohexanone. This compound was identical with that resulting from the dehydration of 2-methylcyclohexanol followed by reduction. However, the reduction of the semicarbazones of pure 2- and 3-methylcyclohexanones by a modified Wolff-Kishner procedure produced a methylcyclohexane with different physical constants. This latter compound was relatively unstable and on standing for several days or on warming changed over into the other form of methylcyclohexane.

If a 1,1-disubstituted cyclohexane has the rigid "chair" structure then interchange of the substituents will give a molecule different from the original compound. If the original substance has the flexible structure, the interchange will make no difference. To test this, Wightman (10) converted 1-carbomethoxycyclohexylformic acid into 1-carbomethoxycyclohexylformamide by two methods, one involving the conversion of the carboxyl group to the amide and the other the conversion of the ester group to the amide followed by esterification of the carboxyl. The two compounds were found to be identical, showing that in this series of derivatives the "chair" form of the cyclohexane ring does not exist as a static modification.

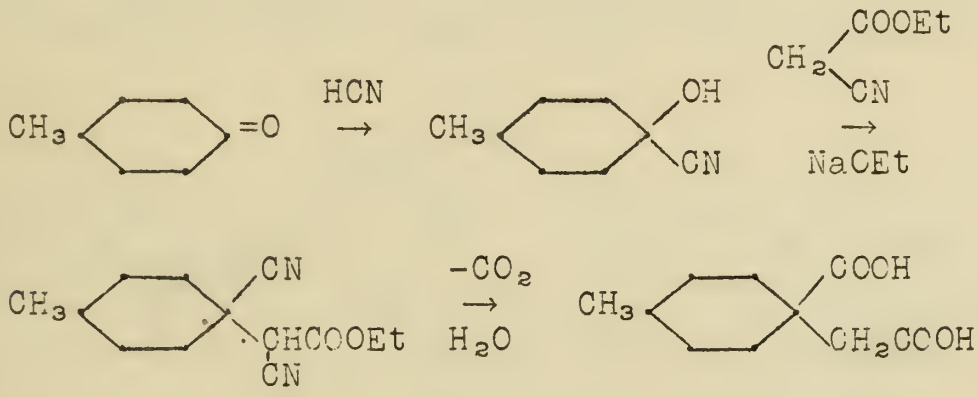
4-Methyl-1-carboxycyclohexylacetic acid is a compound of the type abC_6H_8cd and possesses <u>cis</u>-<u>trans</u> isomerism of the classical type. On the basis of strainless rings, six isomers are possible. Qudrat-I-Khuda (11) claims to have isolated four forms of this compound. Other investigators (12,13) could not confirm these results



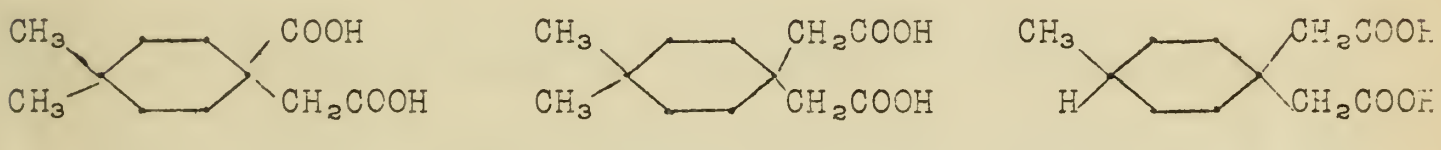
and assumed that at least two of the forms were mixtures. Qudrat-I-Khuda also synthesized the corresponding <u>m</u>- and <u>o</u>-methyl

compounds by the same general procedure and reported the isolation of four isomers in every case.

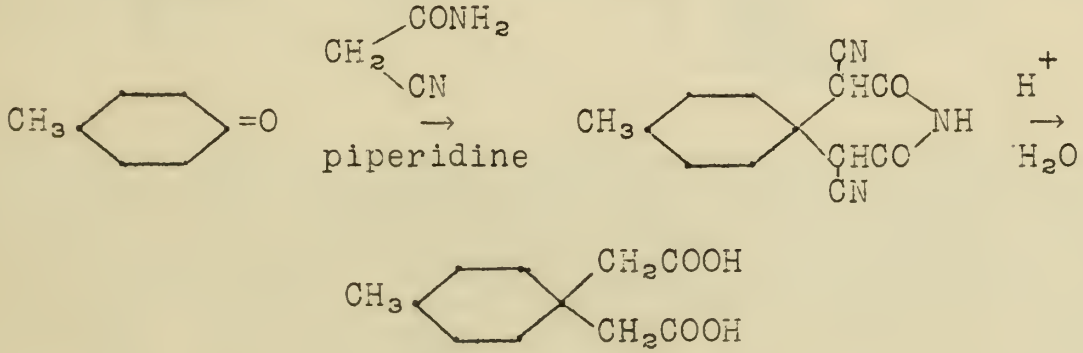
Desai and coworkers (12) also synthesized the 1-carboxy-4-, 3-, and 2-methylcyclohexylacetic acids by the same method and by the one shown below but in each case isolated merely the two isomers expected on the basis of cis-trans isomerism.



To eliminate the complications of cis-trans isomerism, Miller and Adams (1) synthesized the following analogous compounds. The



4,4-dimethyl-1-carboxycyclohexylacetic acid was synthesized by the method of Qudrat-I-Khuda. The 4,4-dimethylcyclohexane-1,1-diacetic acid and the 4-methylcyclohexane-1,1-diacetic acid were synthesized in the following manner. In each case only one form of the com-



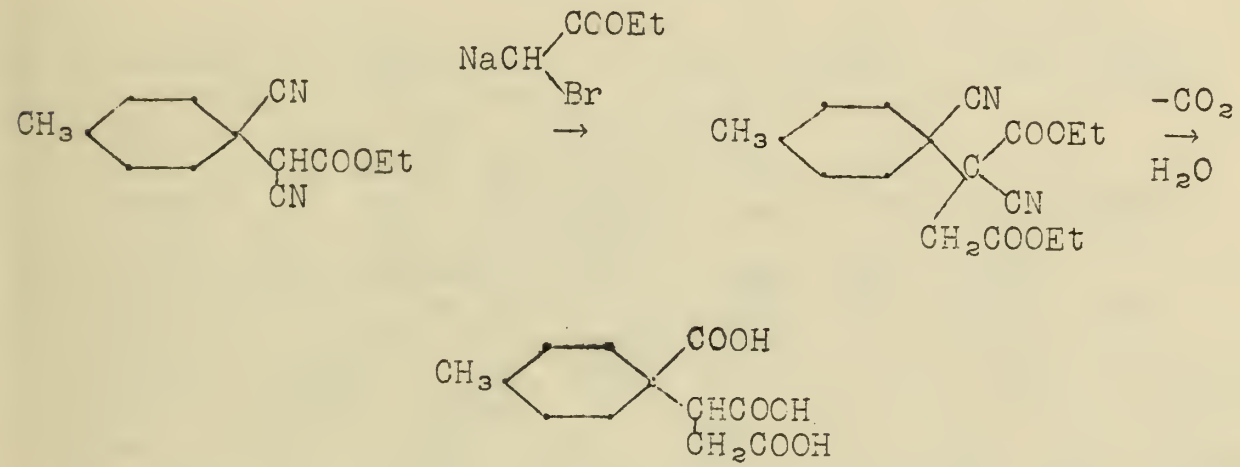
pound could be isolated though a careful search was made.

Desai and coworkers (12) have synthesized many substituted cyclohexanes in an attempt to find substituents which will stabilize the "chair" and "boat" forms.

By the condensation of aryl amines with cyanohydrins of the methylcyclohexanones, arylaminoethylcyclohexanes were prepared by these workers but only two isomers resulted in each instance.

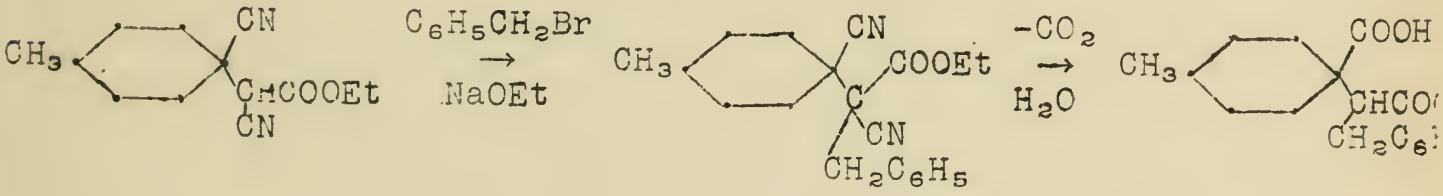
In the hope that the damping effect of a dimethyl group might facilitate the isolation of strainless isomers, 1-carboxy-3,3-dimethylcyclohexane-1-acetic acid was synthesized. Only one form of the product could be detected.

Desai then prepared the 1-carboxy-4-, 3-, and 2-methylcyclohexane-1-succinic acids. Again, only two isomers were obtainable

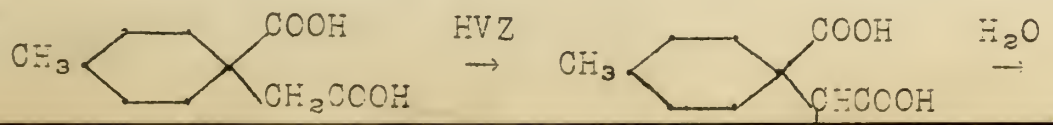


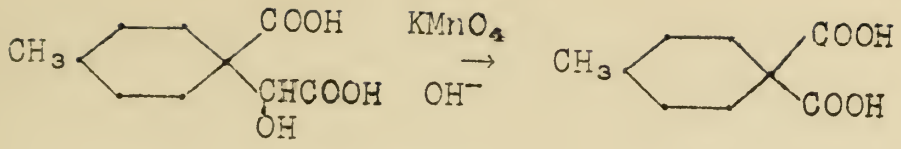
which does not necessitate the assumption of a multiplanar ring.

The 1-carboxy-4- and 3-methylcyclohexane-1-benzylacetic acids were also synthesized. The products occurred in but two isomeric forms.



However, Desai claims to have succeeded in isolating two isomers of 4- and 3-methylcyclohexane-1,1-dicarboxylic acids, in which there is no possibility of ordinary cis-trans isomerism. As mentioned previously, 4-methyl-1-carboxycyclohexylacetic acid can be separated into two isomers which were assumed to be cis and trans forms. By converting the acetic acid group to a carboxyl group in each of these isomers Desai obtained two different compounds. Since the possibility of cis-trans isomerism is eliminated by this procedure, he advances this as evidence for the strainless forms of the cyclohexane ring. The method he used is the following.





The acceptance of this work must await confirmation.

Bibliography

1. Miller and Adams, J. Am. Chem. Soc., 58, 787 (1936).
2. Schomaker and Stevenson, J. Chem. Phys., 8, 637 (1940).
3. Rasmussen, J. Chem. Phys., 11, 249 (1943).
4. Vogel, J. Chem. Soc., 1938, 1323.
5. Schrauth and Görig, Ber. 56B, 1900 (1923).
6. Kursanoff, J. Russ. Phys. Chem. Soc., 34, 221 (1902).
7. Wallach, Ber., 40, 70 (1907).
8. Zelinskii and Tarassova, Ber., 65B, 1249 (1932).
9. Cowan, Jeffrey, and Vogel, J. Chem. Soc., 1939, 1862.
10. Wightman, J. Chem. Soc., 1926, 2541.
11. Qudrat-I-Khuda, J. Ind. Chem. Soc., 8, 277 (1931); 15, 462 (1938); 15, 489 (1938).
12. Desai, et al, J. Chem. Soc., 1936, 416, 1159, 1162; 1939, 84; Proc. Ind. Acad. Sciences, 14, 516 (1941); 15, 168 (1942).
13. Goldschmidt and Gräfinger, Ber., 68, 279 (1935).

Reported by Carl J. Claus
May 16, 1947